ASPECTS OF THE PREVENTION AND TREATMENT OF OESOPHAGEAL CANCER

by

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CONTENTS

PART TWO: THE STUDIES

Abstract

This thesis comprises three studies that examine the prevention and treatment of oesophageal cancer.

Barrett's oesophagus is a pre-malignant condition. It is an attractive idea that successful eradication of Barrett's oesophagus could reduce the risk of development of an oesophageal carcinoma. In the first study 12 patients with at least two centimetres of specialised intestinal metaplasia were treated with Argon Plasma Coagulation. Multiple biopsies were taken at baseline, and at two and six months following treatment. These biopsies were analysed for histology, p53 immunostaining, and cell cycle abnormalities using flow cytometry. On follow-up there was a trend for an increase in the number of squamous biopsies and a decrease in the number of biopsies showing intestinal metaplasia. Three patients developed persistent buried glands and a fourth patient developed an oesophageal carcinoma during follow-up. There was no significant change in follow-up of either the p53 staining or the flow cytometry.

Only about a third of patients presenting with oesophageal cancer are suitable for curative surgery. For the remainder, the aim of therapy is palliation of malignant dysphagia and maintenance of a reasonable quality of life. The second study is a randomised trial comparing the use of Nd:YAG laser therapy or insertion of an expandable metallic stent in 52 patients for the palliation of malignant dysphagia. Patients were assessed prior to treatment and thereafter at two monthly intervals for assessment of dysphagia and quality of life using the SF36, HAD and EORTC-QLQC30-OES-24 questionnaires. The laser patients survived significantly longer than the stented patients, but this must be balanced against the increased cost of the

laser therapy. Palliation of dysphagia was disappointing but did not differ between the two groups. Quality of life was globally impaired in both groups at baseline. Notably the stented patients had significantly more pain than the laser patients at the two month follow-up.

The last study retrospectively examines the effect of radical radiotherapy on a cohort of 60 patients with oesophageal cancer. This study revealed a one year survival of 40% and a five year survival of 0%. Half of patients experienced complications during the treatment and a further 25% had post-radiation complications. Radical radiotherapy can no longer be considered as appropriate therapy for oesophageal cancer.

Oesophageal carcinoma is rapidly rising in incidence and is requiring increasing expertise and resources. Further studies need to focus on optimising and evaluating ablative techniques for Barrett's oesophagus and palliative treatments for oesophageal cancer.

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ABBREVIATIONS

5-ALA	5-Aminolevulinic Acid
APC	Argon Plasma Coagulation
CDK	Cyclin Dependent Protein Kinases
CLO	Columnar Lined Oesophagus
EBRT	External Beam Radiotherapy
EGF	Epidermal Growth Factor
EORTC-QLQC30-OES24	European Organisation of Research on Treatment Quality of Life Questionnaire with Oesophageal module.
HAD	Hospital Anxiety and Depression Scale
HP	Helicobacter pylori
HRA	H2 Receptor Antagonists
HRQOL	Health Related Quality of Life
GORD	Gastro-Oesophageal Reflux Disease
Mls	Millilitres
Nd:YAG	Neodynium-Ytrium-Aluminium-Garnet Laser
PCNA	Proliferating Cell Nuclear Antigen
PDT	Photodynamic Therapy
PPI	Proton Pump Inhibitor
QOL	Quality of Life
SD	Standard Deviation
SF36	Short Form 36
TGF	Transforming Growth Factor

DECLARATION

I declare that the work contained in this thesis is original. I have been solely responsible for the organisation and day-to-day running of the studies contained herein, as well as all aspects of data collection and the analysis of results, unless otherwise referenced.

Helen J Dallal

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PART ONE: INTRODUCTION & LITERATURE REVIEW

CHAPTER 1-Barrett's oesophagus (A critical review of the literature)

1.1 Introduction

This thesis concerns aspects of oesophageal neoplasia. This includes a spectrum of disease ranging from Barrett's oesophagus, recognised as the most important pre-malignant condition, to therapy for established cancer.

The term 'Barrett's oesophagus' is still widely used, but the entity now recognised in clinical practice differs substantially from Barrett's original description. Several alternative terms have been suggested; these are based upon histological features, but none is perfect, many are clumsy and none have achieved universal acceptance. Problems of definition are addressed in more detail in the next section, but despite its limitations, 'Barrett's oesophagus' is used in this thesis, since this term is recognised by clinicians, pathologists and scientists.

1.2 History

Tileston first described the appearance of a columnar-lined oesophagus in 1906 [1]. The eponym Barrett's oesophagus has been widely used since 1950, when Norman Rupert Barrett, an eminent British surgeon, defined the oesophagus as " that part of the foregut, distal to the cricopharyngeus sphincter, which is lined by squamous epithelium" [2]. He had also observed that in a number of patients the distal end of what he presumed to be the oesophagus was lined with gastric-type columnar epithelium. He suggested that in such patients, the squamous oesophagus was

congenitally short, resulting in the tethering of a tubular part of the stomach within the chest. Bosher and Taylor were the first to describe goblet cells in the columnar lined oesophagus [3]. The following year, Morson and Belcher described an oesophageal adenocarcinoma adjacent to mucosa tending towards an intestinal type and containing goblet cells [4].

A further report argued that the whole of the tubular intrathoracic structure described by Barrett, anatomically and pathologically resembled the oesophagus rather than the stomach because it had no peritoneal covering, had submucosal glands and muscularis propria [5]. A few years later in 1957, Barrett accepted this argument and suggested that the condition should be called " lower esophagus lined by columnar epithelium" [6]. Nonetheless, the term Barrett's oesophagus has remained.

Although most authors writing during the 1950s observed an association with oesophagitis, they still assumed that the columnar lined oesophagus was congenital. Moersch was the first to imply that the columnar lined oesophagus was an acquired condition due to gastro-oesophageal reflux disease (GORD)[7].

Throughout the 1960's and early 1970's there were several controversial reports describing the histology of the columnar-lined oesophagus. Junctional epithelium, fundic type epithelium and intestinal type epithelium with goblet cells were all found lining the oesophagus [8];[9]. One study clarified the situation by describing the histology of manometrically guided biopsies taken throughout the length of the oesophagus in 11 patients [10]. These patients were found to have either one or a combination of three types of columnar epithelium lining the distal oesophagus; these were classified as junctional, gastric fundic-like or a type with intestinal

metaplasia within specialised columnar epithelium. The latter was found adjacent to the squamo-columnar epithelium.

The endoscopic diagnosis of Barrett's oesophagus was easy when long segments of columnar epithelium extended well up the oesophagus and so most studies only included such patients. Diagnostic difficulties arose when a biopsy was mistakenly obtained from the columnar epithelium of the proximal stomach, giving a false positive diagnosis of Barrett's oesophagus. This obviously could occur more easily where there was a short segment of Barrett's oesophagus associated with oesophagitis and a hiatus hernia.

In order to avoid this diagnostic dilemma, different investigators used different and arbitrary diagnostic criteria for defining the extent of Barrett's oesophagus. This varied from lengths of two cm to five cm of columnar lined oesophagus [11-13]. Thus, the problem of false positive diagnoses was avoided, but short segments of metaplastic epithelium in the distal oesophagus were not recognised.

Gradually, the association between Barrett's oesophagus and adenocarcinoma was established. In the majority of patients with an adenocarcinoma associated with Barrett's oesophagus, the adjacent mucosa was specialised columnar epithelium, often showing dysplasia [14]. Further studies confirmed that specialised columnar epithelium predisposed to the dysplasia- adenocarcinoma sequence [15]. Investigators interested in the relationship between Barrett's oesophagus and adenocarcinoma therefore opted to give Barrett's oesophagus the histological definition of specialised intestinal epithelium [16;17]. Again arbitrary values were chosen for the length of the specialised epithelium required for the diagnosis.

1.3 Definition and Diagnosis

Several problems exist in defining Barrett's oesophagus either by the extent of the columnar lining or by the presence of intestinal metaplasia. These will be considered in turn.

The ability to define Barrett's oesophagus by the extent of the columnar lining depends on the accuracy of definition and identification of the gastro-oesophageal junction. Unfortunately anatomists, radiologists, physiologists and endoscopists have failed to reach a consensus on how to identify its precise location. Criteria used by anatomists such as the peritoneal reflection are not clinically useful. Physiologists use manometry to identify the lower border of the lower oesophageal sphincter and use this as their definition of the gastro-oesophageal junction. However, the lower oesophageal sphincter is difficult to define endoscopically and one study has shown big differences in the manometric and endoscopic position of the lower oesophageal sphincter [18]. It has been suggested that the gastro-oesophageal junction lies at the point where the tubular oesophagus flares and the proximal margin of the gastric folds begin[12]. In reality the oesophagus is a dynamic organ and its appearance is constantly changing by peristaltic waves. Few studies address these difficulties, and furthermore, there is no gold standard against which to judge the criteria.

If the gastro-oesophageal junction cannot be correctly located, then any estimate of the length of the columnar lining will be inherently imprecise. In addition, if Barrett's oesophagus is defined by imposing some arbitrary length in the diagnostic criteria, patients with shorter segments than this (perhaps with malignant potential) will be ignored.

Others have attempted to define Barrett's oesophagus merely by the presence of specialised intestinal metaplasia, thus drawing away from Barrett's original description. This definition is not without its problems. Intestinal metaplasia of the gastric cardia does occur and if biopsies are accidentally taken from below the gastro-oesophageal junction, an incorrect diagnosis may be made. It is not known whether such intestinal metaplasia has a similar aetiology and prognosis as Barrett's oesophagus, and currently they should be considered separate entities. In addition, intestinal metaplasia may be patchy within a segment of columnar lined epithelium, and sampling error may lead to falsely negative results.

More recently, there has been growing recognition of endoscopically inapparent intestinal metaplasia at the gastro-oesophageal junction. Several studies have been designed to examine this phenomenon. In the earliest study in 1994, consecutive patients had biopsy specimens taken from the squamo-columnar junction irrespective of its appearance and location[19]. Among 142 patients without endoscopically apparent Barrett's oesophagus, 26 (18%) had specialised intestinal metaplasia in the biopsy. Four further studies have confirmed that short, inconspicuous segments of Barrett's oesophagus can be found frequently at the squamo-columnar junction in unselected patients presenting for endoscopy[20-23].

Barrett's oesophagus has been associated with GORD and the development of adenocarcinoma. Only one of many studies reported an association of short segment Barrett's and GORD. Although very short segments of Barrett's oesophagus have been associated with adenocarcinoma, the cancer risk for patients with short segments of intestinal metaplasia in the distal oesophagus is not known [24-26]. Thus, it

may not been justified to include both patients with short and long segments of columnar lined oesophagus under the same diagnostic category.

Spechler has proposed an alternative system of definitions that does not rely upon imprecise endoscopic measurement[27]. Any length of columnar epithelium, observed endoscopically should be referred to as the columnar lined oesophagus, and histology further distinguishes columnar lined oesophagus with specialised intestinal metaplasia from columnar lined oesophagus without specialised intestinal metaplasia. As the risk of adenocarcinoma appears to be related to the length of the oesophageal intestinal metaplasia, it is still important to measure its extent, even though these measurements are imprecise [28]. Spechler suggests that is clinically more valid to use a descriptive definition, for example, columnar -lined oesophagus with 10 cm of intestinal metaplasia, for each patient than simply using the more ambiguous term of Barrett's oesophagus. Where biopsies taken from an apparently normal gastro-oesophageal junction reveal specialised intestinal metaplasia the term specialised intestinal metaplasia at the oesophagogastric junction should apply.

1.4 Epidemiology

Barrett's oesophagus is mainly a disease of the Western male and is rarely reported in the Orient or third world countries. Approximately 12% of patients endoscoped for symptoms of reflux disease will have Barrett's oesophagus. In a population-based study, the clinical prevalence of Barrett's oesophagus was 22.6/100,000 but this rose by 21 fold in an autopsy series [29]. The prevalence of Barrett's oesophagus in unselected dyspeptic patients presenting for endoscopy is approximately 1%[30].

1.5 Aetiology

It is widely assumed, although not proven, that Barrett's oesophagus develops when the normal squamous oesophageal epithelium is replaced by columnar epithelium during the process of healing after an acute injury to the oesophageal mucosa. Acute oesophageal mucosal injury alone, however, is not sufficient to induce columnar cell metaplasia because damaged squamous oesophageal epithelium is usually repaired by squamous epithelial regeneration. A chronically abnormal environment in the oesophagus due to GORD during the process of healing appears to be a prerequisite for the development of Barrett's oesophagus. In most patients Barrett's oesophagus seems to be the result of excessive reflux of gastric acid into the oesophagus which causes the acute mucosal injury and also provides the abnormal environment during the healing phase which predisposes to columnar metaplasia. It is thought that reflux of acid causes inflammatory injury to the squamous epithelium. A multipotential basal cell re-epithelialises the ulcerated area and through continued reflux these may then differentiate into metaplastic epithelium.

This theory is supported by the observation of increased oesophageal acid exposure in over 90% of patients with Barrett's oesophagus, the development and proximal progression of Barrett's mucosa during long-term follow-up of patients with gastroesophageal reflux and the induction of columnar oesophageal metaplasia in experimental models of chronic gastroesophageal reflux [31-36].

Compared with patients with GORD who do not have Barrett's oesophagus, both the quality and quantity of the refluxate appear to be different than in patients with Barrett's oesophagus. Ambulatory 24-hour oesophageal pH monitoring demonstrated a markedly increased frequency and duration of reflux episodes

compared with patients with no columnar metaplasia [37;38]. One study has shown that cisapride may be effective by preventing this reflux [39].

Increased oesophageal acid exposure appears primarily to be due to a reduced lower oesophageal sphincter pressure [37;40-42]. When lower oesophageal sphincter pressures are measured using radially orientated pressure transducers, a mechanically defective sphincter can be documented in over 95% of patients with Barrett's oesophagus [43]. Ineffective oesophageal clearance function due to failure of peristaltic activity within the body of the oesophagus further prolongs oesophageal exposure to gastric content [44]. One study has shown that the propulsion of a bolus in the distal oesophagus and, consequently, clearance of refluxed gastric contents, depends on peristaltic contractions with a minimum amplitude of 30-40mmHg[45]. Both standard and 24- hour manometry of the oesophageal body show an increased prevalence of ineffective oesophageal contractions in patients with Barrett's oesophagus [33;41;46]. Combined 24-hour manometry and pH monitoring demonstrate that, ineffective contractions in the oesophageal body correlate with the prolonged duration of individual reflux episodes [46;47].

Barrett's oesophagus can develop after total gastrectomy and this indicates that reflux of acid is not essential for the development of Barrett's oesophagus [48;49]. Studies in rats have shown that after exposure to a carcinogen oesophageal squamous cell carcinoma will develop. Following an oesophagoduodenostomy (allowing the reflux of duodenal and gastric juices) 30% develop adenocarcinoma, whereas if in addition a gastrectomy is carried out (permitting only duodenal reflux) 87% will develop adenocarcinoma [50]. This suggests a synergism between gastric and duodenal juices; gastric juice being protective and duodenal content carcinogenic.

In contrast, the toxic effect of duodenal reflux on the human oesophagus is less clear partly because of difficulty in measuring the refluxate. Recently, studies using aspiration and chemical analysis of gastric contents have promoted further discussion. Aspiration from the stomach or oesophagus and subsequent chemical analysis of the aspirate permits direct measurement of bile and pancreatic enzyme concentrations. Stein et al have shown that after a meal, total bile acid concentration in the oesophagus was significantly increased in patients with GORD [51]. There was no difference in the quantity or activity of Trypsin between normal volunteers and patients with GORD. In contrast the bile acid concentration in the refluxed gastric juice was markedly increased in patients with a stricture or Barrett's oesophagus compared to normal volunteers.

A fibreoptic system for circadian monitoring of biliary duodeno-gastric and duodeno-gastric-esophageal reflux (Bilitec 2000 System) has been developed by Becchi et al [52]. Kauer et al used this system to evaluate the severity and circadian pattern of bile reflux in a series of patients with GORD [53] Patients with Barrett's oesophagus had a significantly higher prevalence of abnormal oesophageal bilirubin exposure than those with oesophagitis or no injury. They also had a higher bilirubin exposure than those without Barrett's oesophagus. The majority of oesophageal bilirubin exposure occurred when the pH of the oesophagus was between 4 and 7. Another group has also confirmed that patients with GORD complicated by Barrett's oesophagus have a higher bile reflux than patients with uncomplicated GORD [54]. Stein et al have further demonstrated that patients with early adenocarcinoma in Barrett's oesophagus had a significantly higher prevalence of oesophageal bile exposure than patients with Barrett's oesophagus but no adenocarcinoma [55].

The rise in the frequency of oesophageal adenocarcinoma parallels the increased use of H2 Receptor Antagonists (HRA) and Proton Pump Inhibitors (PPI's). It is postulated therefore that chronic acid suppression may therefore be detrimental by allowing reflux of duodenal contents through the alkalinised stomach environment. Whether duodeno-gastro-oesophageal reflux is responsible for the dramatic increase of adenocarcinomas of the gastro-oesophageal junction needs further investigation. If this is the case, future research might include the use of bile binding agents, prokinetic agents and Helicobacter pylori eradication in preventing Barrett's oesophagus and adenocarcinoma. The effect of PPI's on the content of the oesophageal refluxate also needs to be explored.

In addition to environmental factors, a genetic predisposition also appears to contribute to the development of Barrett's oesophagus. Familial occurrence of columnar cell lining of the distal oesophagus has been described in monozygotic and non-identical twins [33;56;57]. However it remains unclear whether genetic abnormalities directly predispose to columnar metaplasia or result in increased gastroesophageal reflux with subsequent development of Barrett's oesophagus [58].

1.6 Risk of oesophageal cancer

Patients with Barrett's oesophagus have an increased risk for the development of oesophageal adenocarcinoma. The relative risk of developing cancer within Barrett's oesophagus is difficult to measure. Prevalence rates of Barrett's associated adenocarcinoma tend to overestimate its true prevalence, as benign disease tends to be asymptomatic.

A number of reports have evaluated the incidence of oesophageal cancer in patients with Barrett's oesophagus. These are summarised in Table 1.1. A distinction should be made between prospective and retrospective follow-up studies. Several of the earlier studies were retrospective, patients with previously diagnosed Barrett's oesophagus were traced years later to find how many had developed clinically diagnosed cancer [59-61]. Prospective studies, in which patients had regular endoscopic follow-up with biopsies, are more likely to include early cancers [62;63]. Short-term follow-up studies may have overestimated the longer-term cancer risk, due to the presence of microscopic adenocarcinomas not detected at initial endoscopy. Retrospective follow-up studies may have underestimated the risk because goblet cell metaplasia was not an entry requirement [59;61]. Patients might have been included who did not have true Barrett's oesophagus.

Several studies have shown that the length of the columnar -lined oesophagus is significantly related to the risk of carcinoma [64;65]. One study showed that a doubling of the length resulted in a 1.7 times increased risk [65]. Iftikar et al also showed that smokers had a 2.3-fold increased risk as compared to non-smokers. Another group found that no patient with a columnar lined oesophagus of less than 8cm developed dysplasia or adenocarcinoma [64].

Identification of dysplasia within Barrett's mucosa identifies patients at increased risk of developing an adenocarcinoma. The presence of dysplasia predates the development of adenocarcinoma. Neoplastic progression in Barrett's oesophagus develops within the metaplastic columnar epithelium when genetic changes occur that lead to the development of dysplasia. Dysplasia is neoplastic epithelium that remains confined within the basement membrane of the epithelial surface. The

accumulation of additional genetic changes within the dysplastic epithelium may lead to the development of adenocarcinoma.

At initial endoscopy, dysplasia is found in 11-37% of all cases of Barrett's oesophagus. [10;66;67]. In follow-up, a further 12-18% of the patients will develop dysplasia over a period of 3 to 5 years [66;67]. In one series, as many as 67% of patients with low-grade dysplasia developed high-grade dysplasia or adenocarcinoma [68]. When low grade dysplasia develops, progression to high grade dysplasia is not inevitable, and regression of dysplasia has been reported [66;67]. Although high grade dysplasia can exist for several years before progressing, the majority of patients will eventually develop adenocarcinoma [66;67]. In a number of retrospective studies, dysplasia was present in the histological specimens of 35-91% of patients with oesophageal adenocarcinoma [13;69;70]. Furthermore, high-grade dysplasia is strongly associated with foci of adenocarcinoma [70-74]. In a recently published series, eight of 11 patients (73%) who underwent surgical resection because of high-grade dysplasia had invasive adenocarcinoma in the resection specimen [75]. In a second series, 13 of 30 patients (43%) undergoing surgery for severe dysplasia had an invasive adenocarcinoma found in the resected oesophagus [76].

Table 1.1(1) Studies examining cancer risk in Barrett's oesophagus

AUTHOR AND YEAR	Number of patients	Mean follow-up time (years)	Incidence of adenocarcinoma (patient -year incidence)	Definition of Barrett's oesophagus	Prospective?
1] van der Veen AH 1989 [60]	166	12	1/170	At least 3cm of columnar lined oesophagus	No
2] Spechler SJ 1984 [59]	105	3.3	1/175	At least 3cm of columnar oesophagus or any length of intestinal metaplasia. 64% had IM.	No
3] Cameron AJ 1985 [61]	104	8.5	1/441	At least 7cm of columnar oesophagus of any sort.	No
4] Hameeteman W 1989 [69]	50	5.2	1/52	At least 3cm of columnar oesophagus. 68% with intestinal metaplasia	Yes
5] Wright TA 1996 [62]	166	2.9	male 1/59 female 1/167	Either 3cm columnar lined oesophagus or 0-3cm of intestinal metaplasia	Yes
6] Drewitz DJ 1997 [63]	177	4.8	1/208	Any length of columnar oesophagus with intestinal metaplasia	Yes
7] Achkar and Carey 1988 [77]	62	2.6	1/166	At least 2cm columnar oesophagus	No
8] Robertson 1988 [78]	56	2.9	1/56	At least 5cm columnar oesophagus 89% Intestinal metaplasia	Yes
9] Ovaska 1989 [79]	32	6.7	1/55	At least 3cm of columnar oesophagus	No

Table 1.1(2) Studies examining cancer risk in Barrett's oesophagus

AUTHOR AND YEAR	Number of patients	Mean follow-up time (years)	Incidence of adenocarcinoma (patient -year incidence)	Definition of Barrett's oesophagus	Prospective?
10] Sampliner 1985 [80]	25	3.7	1/56	At least 2cm of columnar lined oesophagus	No
11] Williamson 1991 [81]	176	2.8	1/99	At least 3cm of columnar lined oesophagus	No
12] Sprung 1984 [82]	41	4.0	1/81		
13] Weston AP 1997 [83]	29	1.8	1/52	At least 2 cm of intestinal metaplasia	Yes
14] Polepalle SC 1990 [84]	312	4.1	1/150	Not Available	
15] Borrie J 1976 [35]	45	22	0	All had a hiatus hernia. Columnar lined oesophagus	No
16] Bonelli [85]	71	3	1/55	100% with intestinal metaplasia	Yes
17] Miros 1991[67]	81	3.6	1/96	At least 3cm columnar lining. 78% with intestinal metaplasia	Yes
18] Iftikar 1992[64]	102	4.2	1/115	At least 5cm columnar lining. 100% with intestinal metaplasia.	Yes

1.7 Screening and surveillance

Barrett's oesophagus is the most important risk factor for the development of oesophageal adenocarcinoma. As this has the most rapidly increasing incidence of any cancer in the USA and UK, a surveillance programme is attractive [86-88]. Oesophageal cancers have a long, asymptomatic growth phase and it is assumed that surveillance will allow early detection and treatment of adenocarcinoma and will improve the prognosis. Numerous factors impact on the efficacy of surveillance in Barrett's oesophagus. These include the natural history of Barrett's and adenocarcinoma, the costs and complications of endoscopy, the cost and mortality and morbidity of oesophageal resection.

To estimate the potential benefit of surveillance, we need to know what the outcome might have been without surveillance. The best way to do this would be a controlled, randomised prospective study comparing surveillance versus no surveillance. This, however, would be a massive undertaking and seems unlikely to happen. The incidence of cancer in Barrett's oesophagus is a critical factor in predicting benefit from surveillance. As indicated above the assessment of cancer risk is in itself full of difficulties, and varies considerably between studies (Table 1.1). Additionally, a sizeable percentage of patients with known Barrett's oesophagus are not suitable candidates for oesophagectomy because of age or concurrent disease, and early diagnosis is unlikely to significantly affect their outcome, unless strategies for local, non-surgical treatment can be developed. Patients undergoing surveillance may still die of oesophageal cancer or complications of resectional surgery.

In one of the largest studies from the Netherlands, 155 patients seen between 1973 and 1986, but not entered into a surveillance programme, were traced in 1994 [89].

Seventy-nine had died, but death was only related to oesophageal cancer in two cases (2.5%), one from metastases and one from postoperative complication. Six further cases had oesophageal cancer, three of who were still alive following oesophageal resection, and the other three had died of unrelated causes. These authors concluded that their patients would not have benefited from an endoscopic surveillance programme.

Wright et al reviewed data from a surveillance programme of 166 patients with Barrett's oesophagus who underwent annual endoscopic surveillance [62]. Six patients had developed cancer. The screened group had a significantly earlier stage than a control group of unscreened cancers. In a more recent study a clinicopathological comparison was made between patients who initially presented with oesophageal adenocarcinoma and those in whom the cancer had been detected during surveillance of Barrett's oesophagus [90]. They showed that surveyed patients had significantly earlier stages and improved two year survival than non-surveyed patients.

The cost of surveillance programmes has been estimated. In the study by Wright et al, the cost of detecting one cancer was £14 868 for men and £42 084 for women [62]. Another American study using retrospective data estimated that the cost of detecting one cancer through an annual surveillance scheme would be $62,000 [77]. Costs would in both cases now be considerably higher.

Provenzale et al performed a decision analysis study to assess the efficacy of surveillance in Barrett's oesophagus on the basis of a cancer risk of 1 cancer per 75 patients-years of follow-up [91]. They concluded that when both quality and length of life were considered, endoscopy every 2-3 years would be the most effective policy,

although this would be very expensive. Endoscopy every 5 years would increase life expectancy with a cost effectiveness similar to other common medical practices. They also pointed out that if the cancer incidence were less that 1 in 200 patient years, no surveillance would be the preferred strategy, because the risks of surveillance and oesophagectomy outweighed any benefit in length and quality of life. This study has received much criticism for making unsubstantiated assumptions. For example, they assume a resection rate of 49% for unscreened cancers and a 75% resection rate for screened cancers. They also assume only a 64% five year survival for cancers detected by the screening programme.

Further problems in the diagnosis of dysplasia through a surveillance programme relate to sampling error. Dysplastic mucosa may occupy most or the entire oesophagus or it may be limited in extent. Thus, the endoscopist must thoroughly sample the mucosa in order to avoid missing small areas of dysplasia or carcinoma. Four-quadrant biopsies at intervals of 2cm or less throughout the length of the Barrett's segment, combined with additional biopsies of any endoscopic lesions produces excellent correlation between the pre-operative endoscopic diagnosis and the final diagnosis in the resected specimen [92,93].

If surveillance is to be recommended, how frequently should this be undertaken? Until recently most authorities would have advised annual endoscopic surveillance, however this has now shifted and recommends screening frequencies between 2-5 years as long as there is no focal abnormality on endoscopy and no dysplasia on biopsy [94,95]. Of concern with such a policy is the possibility of interval cancers. Indeed one study has shown that 50% of the cancers detected by an annual surveillance programme were detected after less than two years [62].

Currently, most oesophageal adenocarcinomas are found in individuals not known to have Barrett's oesophagus. Most cases of Barrett's oesophagus are unrecognised, and therefore surveillance of patients with known Barrett's oesophagus will have a minimal impact on the overall death rate of oesophageal carcinoma. Only one case of Barrett's oesophagus in 20 is detected in life [29]. As about 10% of adults have symptoms of GORD, a large population of patients is at risk for developing or harbouring Barrett's oesophagus. The prevalence of Barrett's oesophagus in patients with GORD is about 12%[42]. Two studies have confirmed that this figure is even higher in patients with complicated reflux disease, such as oesophagitis or stricture [42;96]. Previous work has suggested that the longer a patient has GORD symptoms the greater likelihood of having Barrett's oesophagus [97;98]. These findings have lent support to the recommendation of many experts to limit screening for Barrett's oesophagus to patients with reflux symptoms of 5-year duration or longer [99]. Reluctance for screening for Barrett's oesophagus is also related to the necessity for endoscopy and biopsy to establish the diagnosis.

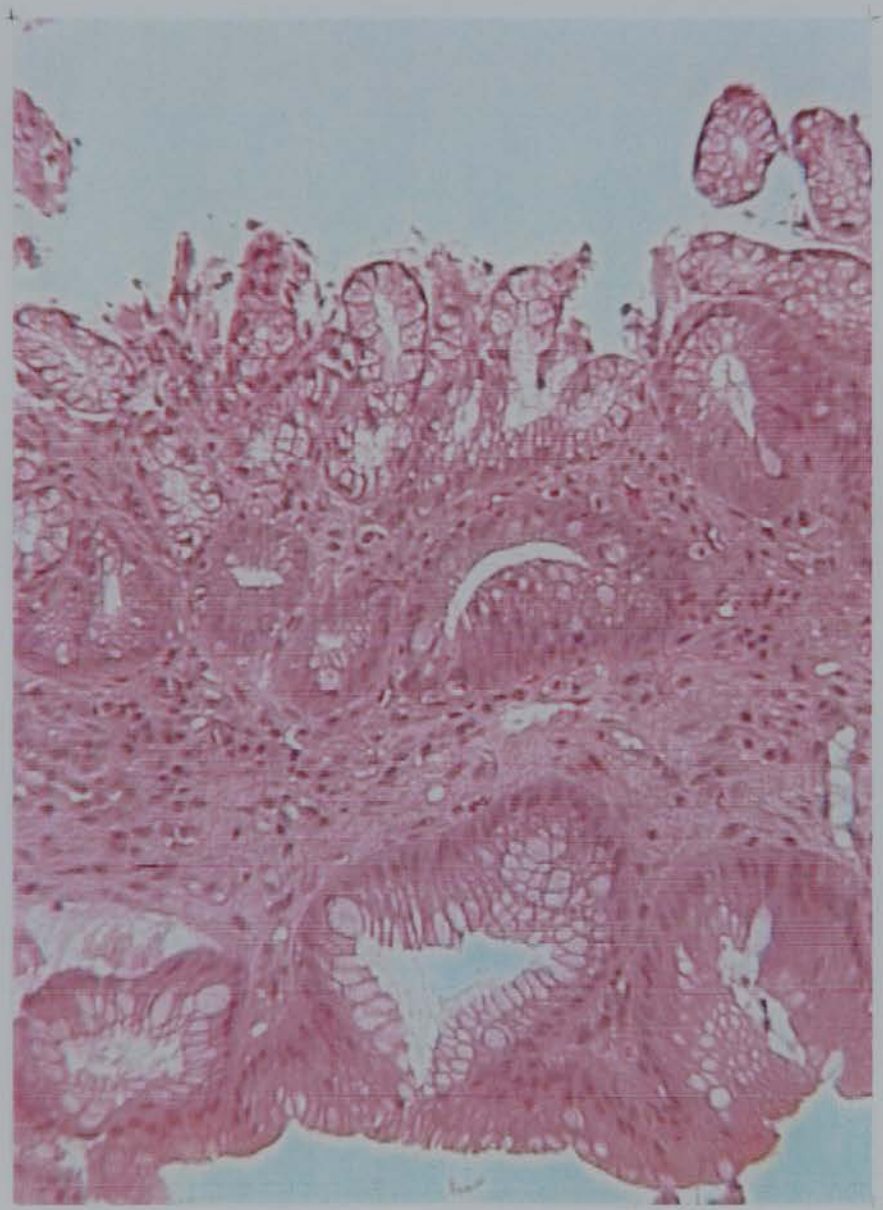
1.8 Histology

Barrett's oesophagus is confirmed when biopsies reveal columnar epithelium on histological examination. Three histological types of Barrett's epithelium have been described: a specialised 'intestinal' type with villous architecture and goblet cells (Figure 1.1); a gastric fundic type with both chief and parietal cells; and a cardiac type with simple mucous glands, but no other features [10]. Specialised intestinal epithelium is a pre-malignant, metaplastic change [13;69], whilst identification of

cardiac or fundic columnar metaplasia has a considerably lower risk for malignant transformation.

Dysplasia is defined as unequivocal neoplastic transformation which is distinguishable from reactive and regenerative change. It is classified by guidelines used for assessment of colonic dysplasia in inflammatory bowel disease, and modified for application to the oesophagus [100,101]. A diagnosis of dysplasia is based on the severity of both architectural and cytological transformation indicating neoplastic transformation. Architectural changes include budded, branched, crowded or irregularly shaped glands. Low grade dysplasia is characterised by nuclear pleomorphism, hyperchromatism and loss of nuclear polarity, but with limited nuclear stratification. High-grade dysplasia is manifest as loss of nuclear polarity, increased nuclear-cytoplasmic ratio, increased mitosis, nuclear hyperchromatism, with crowding and stratification of nuclei extending from the basement membrane to the luminal surface. The diagnosis of dysplasia and its varying degrees of severity may differ between pathologists. In a study of eight experienced pathologists, there was an 86% interobserver agreement over the diagnosis of high-grade dysplasia, but a diagnosis of dysplasia or low-grade dysplasia was more variable with only 58 and 75% agreement respectively [102]. Therefore it is recommended that two independent pathologists should confirm the diagnosis of dysplasia.

Figure 1.1 Pathology slide of Barrett's epithelium with specialised intestinal metaplasia (x25 magnification)



For this reason, researchers have searched for a better indicator for risk of malignant change in columnar- lined oesophagus, largely using flow cytometry to look for changes in DNA ploidy and either immunohistochemistry or polymerase chain reaction (PCR) to look for p53 gene abnormalities.

1.9 Molecular and cytological events in the development of Barrett's oesophagus

1.9.1 p53

Lane and Crawford first discovered the p53 gene in 1979. The journal "Science" named it in 1993 [103]. p53 has a role in the regulation of the normal cell cycle and in tumorigenesis [104].

1.9.1.1 Action of p53 in Normal Cells

The normal cell cycle consists of four phases Mitosis (M phase), a gap (G1), DNA synthesis (S phase), and another gap (G2). G1 is a variable period when the cell is actively functioning; cells may enter the proliferating cell cycle or become dormant. In the S phase, DNA replication occurs. G2 is the brief phase when the cell prepares for the initiation of mitosis. The M phase represents mitosis in which identical genetic material is apportioned to daughter cells.

p53 regulates the cell cycle and loss of this regulation through p53 malfunction contributes to many cancers. p53 appears to act as a "guardian of the genome" by behaving as a tumour suppresser gene and transcription factor. DNA damage upregulates p53 which then stops the cell cycle at the G1-S checkpoint and

stimulates DNA repair. p53 slows the cell cycle by acting as a transcription factor for Wild-type activated fragment 1(WAF1) whose product (p21) regulates cyclin dependent kinases. Binding of p21 to cyclin-dependent kinases leads to a slowing of the cell cycle at the G1-S transition. p53 stimulates DNA repair through its interaction with ERCC3 (Xeroderma pigmentosum group B or XPB) and a growth arrest and DNA damage inducible gene (GADD45). However, if DNA damages too severe, p53 pushes the cell into programmed cell death (apoptosis).

1.9.1.2 Failure of p53

Failure of p53 results in loss of the G1-S checkpoint and of the p53 promoted DNA repair mechanisms. Loss of p53 function occurs when cells are in transition from the precancerous state to overt cancer.

For p53 to fail, both of its alleles must be eliminated The most common way to lose the effect of both alleles is to destroy the function of one by a mutation and to remove the second allele entirely from the other chromosome. However, a p53 mutation in only one allele without loss of the other may still cause loss of normal p53 function. p53 proteins join together in vitro. If one p53 member of the complex is abnormal, the whole complex will not function correctly. As mutant p53 usually has a longer half- life than the wild-type protein, transcription at the same rate results in accumulation of the mutant p53. Thus, most of the p53 complexes will then contain mutant p53 and be inactive. This is called the dominant negative effect. This accumulation is the basis for the immunohistochemical detection of p53 protein overexpression.

1.9.1.3 Measurement of p53 and p53 mutations

p53 gene alterations can be studied by a variety of techniques including the polymerase chain reaction (PCR) and sequence analysis or by single stranded conformation polymorphism analysis (SSCP). Overexpression of p53 protein can also be detected by immunohistochemical staining for specific anti-p53 antibodies. Theoretically, p53 overexpression is an indirect method of detecting a p53 gene mutation, although some studies have shown that not all p53 mutations cause p53 protein overexpression and that p53 overexpression may exist without a p53 mutation. One study examined p53 mutations and p53 overexpression in 10 patients with Barrett's metaplasia alone and 10 with Barrett's metaplasia and carcinoma. In the first group, one out of three patients who were p53 positive showed no p53 gene mutation and three out of five patients who had a p53 mutation were negative for p53 protein overexpression. In the second group, four out of six patients positive for p53 showed no p53 gene mutation [105]. Another study has also measured both p53 overexpression and p53 mutations in 17 patients with oesophageal adenocarcinoma [106]. One patient was p53 positive but showed no detectable p53 gene mutation, whilst five patients had a detectable mutation without evidence of p53 overexpression. These latter patients showed a chain-terminating mutation, resulting in the synthesis of a truncated protein that was not detectable by immunohistochemistry.

1.9.1.4 p53 immunoreactivity in Barrett's oesophagus

The appearance of p53 protein in Barrett's oesophagus and oesophageal carcinoma has been well documented by several investigators. In Barrett's oesophagus

complicated by adenocarcinoma, p53 overexpression has been found in 53% to 87% of specimens.

In one study, a p53 mutation was found in 92% of patients with oesophageal carcinomas, whereas, overexpression of p53 protein was only detected in 62% of patients [107]. In a later study, p53 mutation was found in only 55% of patients with oesophageal carcinoma [108] Ramel et al measured p53 using flow cytometry in patients with Barrett's oesophagus and adenocarcinoma in relation to the histological grade [109]. He found p53 to be positive in the 5% of patients who did not have dysplasia, in 15% of patients with indefinite/low grade dysplasia, in 45% of patients with high grade dysplasia and in 53% of patients with adenocarcinoma. Another study has shown that in patients with a p53 positive adenocarcinoma, p53 overexpression only occurs in the adjacent mucosa in the presence of severe dysplasia [110]. Younes et al undertook immunohistochemical staining for p53 in Barrett's epithelium in 54 patients [111]. In 114 specimens they observed positive p53 in Barrett's epithelium in 0%, 9%, 55% and 87% of specimens interpreted as negative for dysplasia, indefinite/low-grade dysplasia, high-grade dysplasia and adenocarcinoma respectively. In a follow-up analysis of 24 patients, positive staining was observed at the time of progression to high grade dysplasia in two out of three patients, one of whom was originally p53 positive but with indefinite/low grade dysplasia.

Campomnosi et al examined p53 and k-ras gene alterations in 30 patients with Barrett's oesophagus [112]. None of the cases showed K-ras mutations whereas 12 patients showed p53 mutation. This mutation was significantly associated with

intestinal metaplasia. This finding may explain why intestinal metaplasia is most closely associated with the development of adenocarcinoma.

Polkowski et al assessed the clinical value of p53 and Ki67 as a marker for tumour progression in Barrett's oesophagus [113]. Thirty-two specimens were examined with varying degrees of dysplasia. P53 was not detectable in any specimen with no dysplasia, in 1/5 indefinite dysplasia areas, in 6/11 low grade dysplasia areas and in 8/9 high grade dysplasia areas. The frequency of p53 accumulation increased significantly with increasing grade of dysplasia.

1.9.1.5 p53 as a prognostic marker in Barrett's oesophagus

p53 may be useful as a prognostic marker in Barrett's oesophagus. As indicated in the studies above, p53 protein accumulation in Barrett's oesophagus correlates with dysplasia. One recent study has aimed to determine the sensitivity and specificity of p53 accumulation as a marker of malignant potential in Barrett's metaplasia [114]. They showed that five out of nine patients with low grade dysplasia and positive p53 developed high grade dysplasia or carcinoma. Whereas, none out of 16 patients with low grade dysplasia and negative p53 developed high grade dysplasia or carcinoma. The mean follow-up was 40 months. They conclude that p53 is more specific for the development of high grade dysplasia or carcinoma than the presence of low grade dysplasia. They suggest that the sub group of patients that have low grade dysplasia and express p53 should be followed up by regular surveillance. However, not all adenocarcinomas overexpress p53, suggesting that a subset of patients with Barrett's oesophagus will undergo malignant transformation despite negative staining for p53 protein. This has been observed in at least one patient who showed neoplastic

progression without detectable p53 accumulation [111]. Therefore further research into additional prognostic indicators is required.

One recent study has measured anti-p53 antibodies in patients with Barrett's oesophagus or oesophageal carcinoma. p53 antibodies were detected in 4 of 36 patients with Barrett's oesophagus, one of whom later progressed to adenocarcinoma. Out of 33 patients with oesophageal cancer 10 had detectable p53 antibodies, two of whom had them detected prior to the diagnosis of cancer. The authors conclude that those patients with Barrett's oesophagus and oesophageal cancer can develop p53 antibodies that may predate the clinical diagnosis of malignancy. Obviously, a larger population of patients with Barrett's oesophagus needs to be studied to confirm these findings [115].

p53 may prove to be a useful adjunct to histology in assessing which patients with Barrett's oesophagus are most at risk for developing a carcinoma. This may permit more accurate selection of a sub-group of patients who would benefit from a Barrett's surveillance programme. Further research needs to be done in this area.

A variety of novel techniques are being developed to ablate Barrett's oesophagus including laser therapies and photodynamic therapies. The long term effect of these treatments and whether they are able to halt neoplastic progression in Barrett's oesophagus is unknown. In particular, changes in p53 expression following such treatments have not been explored.

1.9.2 Flow cytometry

Flow cytometry is based on the stoichiometric reaction of fluorescent dyes with DNA. Cells in the G0/1 phase have a diploid amount of DNA. , cells undergoing mitosis have a double diploid amount and those in S phase have an intermediate amount. If cells contain an abnormal amount of DNA (aneuploid) they can also be detected. Flow cytometry was originally used to assess cell numbers and size. It was subsequently developed to quantify nucleic acid concentration using the absorption and scatter of light. Mullaney et al produced the first DNA histogram with clearly defined G0/G1, S, G2 and M phases [116]. This discovery enabled the quantification of a number of parameters on a large number of cells giving rapid and reproducible results.

Flow cytometry depends upon the preparation of a single cell suspension, necessitating grinding of the tissue. The DNA can then be stained, filtered to remove clumps and syringed to break up small aggregations. The stained cell suspension is injected into the flow cell of the flow cytometer where it is hydrodynamically focused to pass through the interrogation point, excitation taking place in either an enclosed quartz flow cell or in air. The cell interacts with the laser light (emitted at 488nm), scattering it in all directions; light scattered in a forward direction is related to the size of the cell, and that at 90 degrees to the amount of refraction of its internal structure. Analogue electrical signals are generated for each particle and converted into digital signals for processing by the computer software to generate parameter correlated histograms. Many different dyes can be used. In this study propidium iodide was used: when excited at 488nm it emits light in the red spectrum at 589nm. The intensity of the red light emitted by the excited nuclei correlates to

the amount of DNA in the nucleus. A photomultiplier tube, which amplifies the signal prior to converting it to a digital pulse, senses the red light. The accumulated pulses from a sample area are then used to generate a histogram.

1.8.2.1 Flow cytometry and Barrett's oesophagus

The evolution of Barrett's mucosa to adenocarcinoma is frequently associated with the development of large changes in the DNA content (ploidy) of the epithelial cells. This can be detected by flow cytometry. All cells in the body, except germ cells are diploid. In normal tissue, most of the cells are in the G0 phase and are shown as a 2N peak when analysed by flow cytometry. In this situation, less than 5-10% of cells show a 4N peak as a result of being in the S or G2 phase of cell division. Abnormalities are identified either by an increased percentage of cells in the 4N phase (S or G2 fraction) suggesting rapid cell division, or by the presence of one or more aneuploid peaks, when >2.5% of the cell nuclei demonstrate abnormal DNA content (>2N).

Flow cytometric abnormalities have been demonstrated in all grades of Barrett's metaplasia from non-dysplastic tissue to adenocarcinoma.

In the first report in 1987, aneuploidy was found in 5.5% of normal patients, in 17.2% of patients with Barrett's, in 100% of patients with dysplastic Barrett's and in 83.3% of patients with oesophageal cancer [117]. A second report in the same year reported either aneuploidy or an increased G2 fraction in 0/18 normal patients, in 2.9% of patients with Barrett's metaplasia, in 25% of patients with indefinite or low-grade dysplasia, and in 100% of patients with high-grade dysplasia or Barrett's adenocarcinoma [118]. In a subsequent report similar results were reported as

indicating an association between the presence of flow cytometry abnormalities and increasing dysplasia [119].

Rabonovitch et al showed that one or more aneuploid cell populations was commonly identified in oesophageal adenocarcinoma [120]. Of 14 patients with Barrett's adenocarcinoma 12 had at least two aneuploid cell populations and four patients had more than 10 aneuploid cell populations. They found a variable concordance between grade of dysplasia and aneuploidy, showing that aneuploidy could be found in a proportion of patients without dysplasia. Another study, which analysed 69 biopsies obtained from 19 patients with Barrett's oesophagus, confirmed these findings [121]. Dysplasia occurred in the absence of flow cytometric abnormalities and, conversely, the latter could be present in the absence of dysplasia. These observations are important since they raise the possibility that flow cytometric abnormalities may be a determinant of cancer risk independent of dysplasia or preceding the development of histological changes. In prospective analysis, 62 patients with Barrett's oesophagus were followed up for a mean period of 34 months [66]. Aneuploidy and increased G2 tetraploid fractions were found to predict neoplastic progression. The authors showed that of 49 patients who had no aneuploidy or increased G2 tetraploid fraction none progressed to high-grade dysplasia or adenocarcinoma, while of 13 patients with flow cytometric abnormalities 9 subsequently developed high-grade dysplasia or adenocarcinoma.

Flow cytometry has usually been carried out on fresh biopsy specimens. A recent study has assessed the feasibility of performing flow cytometry on paraffin-embedded biopsies to improve ease of analysis and to allow analysis of archival material [122]. Among the 58 specimens with Barrett's oesophagus, it was possible to

analyse 86%. DNA aneuploidy was identified in 77% with high grade dysplasia, 16% with low-grade dysplasia, 23% of indefinite for dysplasia, and 0% without dysplasia. This shows that routinely processed paraffin-embedded biopsies can be used for flow-cytometric analysis and, in agreement with previous studies, shows a close correlation between DNA aneuploidy and degree of dysplasia.

Flow cytometry has also been assessed as a prognostic indicator for patients undergoing an oesophageal resection for a Barrett's related adenocarcinoma [122]. Flow cytometry, was carried out on paraffin embedded specimens from 40 patients with an adenocarcinoma in Barrett's oesophagus. Although there was no significant correlation between DNA-ploidy, TNM-stage or histological grade of the tumour, DNA-ploidy significantly ($p=0.04$) correlated with survival. Thus, DNA ploidy is an independent prognostic factor for the survival of patients with an adenocarcinoma in Barrett's oesophagus.

Further studies need to be performed to assess the usefulness of flow cytometric abnormalities in predicting neoplastic progression in patients with Barrett's oesophagus. It may also be useful in evaluating the ability of novel ablative therapies to normalise the cell cycle

1.9.3 Cyclins

Cyclins are critically important regulators of the cell cycle. They act primarily by activating cyclin-dependent protein kinases (CDK). Subsequent CDK mediated phosphorylation of specific proteins drives the cycle through particular checkpoints of the cell cycle. There are at least 11 distinct cyclin genes in the human genome that can bind to and activate at least seven CDK's. During normal growth, different

cyclins are expressed at specific times of the cell cycle. For example, cyclin B1 activates CDK1. It begins to accumulate at the time of cell exit from S, reaches a maximum in G2 and breaks down in M.

D type cyclins are involved in the regulation of cell movement through G1 primarily by activating CDK4 which then phosphorylates the retinoblastoma tumour suppression gene protein RB. Phosphorylation of pRB releases E2F factor which activates transcription of the components of the DNA replication machinery, thereby committing the cell to the S phase [123].

Rearrangement, amplification, and/or increased expression of the cyclin D1 gene have been reported in human parathyroid adenomas, B-cell lymphomas, and squamous cell carcinomas of the head and neck. Thus, cyclin D1 may act as a cellular oncogene. It has also been recently reported that overexpression of cyclin D1, similar to mutation of p53 is associated with genome instability [124].

A recent study has shown that cyclin D1 and D3 in normal cell lines are restricted to G1 phase, whereas in tumour cell lines they are also expressed in S and G2/M [125].

Overexpression of the cyclin D1 gene has been found in 32% of human oesophageal squamous cancer lines and in 64 % of oesophageal adenocarcinomas [126,127].

Little research has examined cyclin expression in Barrett's oesophagus. Arber et al have shown that about 46% of Barrett's oesophagus samples showed increased nuclear expression of cyclin D1 protein compared to normal oesophageal mucosa [128]. It has previously been suggested that early neoplastic progression in Barrett's involves at least 3 types of cell cycle abnormality (1) Mobilisation of cells from the G0 phase to G1 (2) Loss of control of the G1-S transition, (3) accumulation in G2

[129]. It is possible that increased cyclin D1 expression in Barrett's may be responsible for these events through its interaction with CDK4 and Rb6 tumour suppresser gene. Thus, increased cyclin D1 expression may be a marker of early malignant change, although other events have to occur for progression to a fully malignant tumour.

1.9.4 Proliferating cell nuclear antigen

Proliferating cell nuclear antigen (PCNA) is an accessory molecule for DNA polymerase and is synthesised in the late G1 and S phases of the cell cycle. It is a marker of cell proliferative activity and hence may be related to metastatic potential. One study examined 93 specimens of Barrett's oesophagus for PCNA [130]. Luminal staining occurred almost exclusively in the specialised Barrett's epithelium versus junctional type epithelium and fundic epithelium. They concluded that PCNA immunolocalization reveals that a high proportion of specialised epithelial cells are proliferating which may explain the association between specialised epithelium and malignancy in Barrett's oesophagus. Gillen et al assessed PCNA expression in oesophageal epithelium from 70 patients with Barrett's oesophagus [131]. They showed that the PCNA index of malignant tissue was significantly different from that of benign and dysplastic specimens. PCNA indices in histologically normal Barrett's epithelium adjacent to a tumour were significantly different from those in normal Barrett's epithelium with no adjacent tumour. In the study of Jankowski et al, the PCNA labelling index was higher in adenocarcinoma (25%) and in Barrett's intestinal type mucosa with high-grade dysplasia (26%) than in intestinal type mucosa without significant dysplasia (20%) and Barrett's gastric type mucosa (12%) [132]. However other studies show conflicting evidence. Jaskiewicz et al examined

PCNA staining in 105 heterotopic biopsies with columnar epithelium [133]. This study showed a close similarity between dysplastic, indefinite for dysplasia and non-dysplastic, mucosal counts. A further study assessing PCNA expression in a group of patients with Barrett's oesophagus who, during follow-up, developed epithelial dysplasia, confirmed this finding [134]. Although there was a remarkable number of PCNA positive cells in high grade dysplasia, there was a considerable overlap in the number of positive cases between low grade dysplasia, indefinite and negative. They concluded that the correlation of PCNA staining with degree of dysplasia is of limited practical use.

1.9.5 Ki67

Ki67 is a murine monoclonal antibody that recognises a nuclear antigen that is expressed in all phases of the cell cycle except G0 and thus is a sensitive marker of cell proliferation. Several studies have measured Ki67 in Barrett's oesophagus. One study showed that measurement of Ki67 was able to distinguish between low and high grade dysplasia [113]. Another study found that the Ki67 labelling index was very low in junctional or gastric type Barrett's epithelium, moderately high in intestinal type epithelium and very high in severe dysplastic epithelium or adenocarcinoma [135].

1.9.6 Abnormal mucus and mucus production

Within dysplastic Barrett's epithelium, there is reduce or absent mucus production. It has also been observed that the cytoplasmic organelles required for mucus biosynthesis are reduced [102]. Lapertosa et al demonstrated the presence of O-

acetylated sialomucins in the goblet cells of specialised columnar epithelium [136]. These were reduced in the mucosa close to a dysplastic area, and completely absent in dysplastic tissue. This loss of O-acetylation suggests a more immature type of epithelium, similar to that of foetal gut, where O-acetylation has not yet taken place. However, as yet there are no data correlating these changes with degree of dysplasia or risk of developing adenocarcinoma. Indeed one study has shown similar amounts of sialomucin staining in dysplastic and non-dysplastic Barrett's oesophagus [133].

1.9.7 Growth regulatory factors

Epidermal growth factor (EGF) and transforming growth factor (TGF) synthesised by the gastrointestinal mucosa bind to epidermal growth factor receptors and regulate the growth and differentiation of the gastrointestinal tract. In Barrett's oesophagus, growth factor activity was significantly higher in dysplastic mucosa, than in non-dysplastic mucosa. [133]. However there was no significant difference between growth factor activity in mucosa showing different grades of dysplasia. Co-expression of EGF or TGF-alpha and EGF-R is associated with autocrine growth regulation in oesophageal carcinoma cells [137]. Barrett's mucosa, particularly when dysplastic overexpress TGF-alpha and EGF-R [136]. TGF-alpha an EGF-R expression were found to be low in junctional or gastric type Barrett's epithelium, and high in intestinal type epithelium, Barrett's epithelium with moderate to severe dysplasia and adenocarcinoma [132;135;137]. Although the increased expression of these growth factors correlates with increasing dysplasia, its independent prognostic value has not been proven by prospective studies.

1.9.8 Chromosomal abnormalities

It has been shown that the development of Barrett's adenocarcinoma is associated with allelic losses of 17p harbouring TP53 and 5q containing APC and MCC. Allelic losses of 17p occur in diploid cells as early events and typically precede the development of aneuploidy and other allelic losses during neoplastic progression in Barrett's oesophagus [138] Allelic losses of 17p or 5q were found in aneuploid cell populations from patients with Barrett's oesophagus who had high -grade dysplasia or cancer [139]. Allelic losses of 17p were found in 92% of Barrett's adenocarcinoma and 5q allelic losses in 77% [140];[141]. It was demonstrated that 17p allelic losses typically occurred before 5q allelic losses during neoplastic progression in Barrett's oesophagus [138];[139].

1.9.9 In vitro experiments

As described above, progression to cancer in Barrett's oesophagus occurs through an accumulation of cell cycle and genetic abnormalities that have been described in vivo. In order to better study neoplastic evolution in Barrett's oesophagus Palanca-Wessel et al have established in vitro cultures from preneoplastic tissues [142]. They successfully established four long-term cultures form 39 attempts. All cultures contained cytogenetic abnormalities and elevated flow-cytometric 4N DNA content fractions. Molecular genetic abnormalities included 17p loss of heterozygosity and p53 mutation in 3 of 4 cultures and 5q loss of heterozygosity in one culture. Inactivation of p53 was statistically associated with successful long-term culture. Such cultures may provide a premalignant in vitro system in which to test potential

therapies for Barrett's oesophagus as well as to examine aetiological factors in neoplastic progression.

1.10 Treatment

1.10.1 Medical and surgical therapy

By definition metaplastic epithelium has the potential to revert to normal [143]. Although both medical and surgical therapy to reduce acid reflux have been reported to induce regression of Barrett's epithelium, these reports have been infrequent and controversial [144-148].

Malesci et al reported regression of Barrett's oesophagus using 60mg of omeprazole every morning for one year. Twelve of the 14 patients had normalisation of pH in the oesophagus. The mean reduction in the length of the Barrett's was 2.4cm with complete regression in two patients [149]. One study has also demonstrated that elimination of reflux symptoms does not ensure that acid exposure is controlled in patients with Barrett's oesophagus [150].

A randomised trial of 59 patients with Barrett's oesophagus has compared medical treatment versus anti-reflux surgery [151]. In the surgically treated group, eight of 32 patients had a decrease whilst three had an increase in the length of Barrett's oesophagus. In the medically treated group two out of 27 patients had a decrease whilst 11 had an increase in the length of their Barrett's oesophagus. Unfortunately, this study has several flaws. At least eight of the 59 patients lacked intestinal metaplasia, and the medical group received omeprazole at an unspecified dose only 10 years after initiation of the study.

To date oesophagectomy provides the only reliable therapeutic option for patients with high-grade dysplasia or early cancer. The high mortality rates, ranging from 4% to 10% in a largely elderly population make this an undesirable procedure [152]. The development of minimally invasive endoscopic therapies for Barrett's oesophagus therefore deserves prime consideration.

1.10.2 Endoscopic therapies

Several different endoscopic modalities have been used to ablate Barrett's mucosa and potentially reduce the risk of cancer. These include Neodynium:Yttrium-Aluminium-Garnet (Nd:YAG) laser thermal ablation, Argon Plasma Coagulation (APC) and Photodynamic Therapy (PDT). One study reports ablation of Barrett's oesophagus in 10 patients treated with high-dose omeprazole and endoscopic multipolar electrocoagulation [151]. The entire Barrett's oesophagus was reversed by visual and biopsy criteria in five of these patients.

1.10.2.1 Photodynamic Therapy

PDT uses the combination of drug and light administered by dye lasers to achieve local tissue destruction. Initially, a photosensitiser is administered intravenously, or orally and is subsequently retained by the precancerous or malignant tissue. Such photosensitisers are non-toxic in their natural state, but when activated by light they become cytotoxic and cause local tissue destruction. The exact means by which this occurs depends on the specific photosensitiser, but it usually relies on the presence of oxygen and the formation of oxygen free radicals. Oxygen radicals are highly reactive and destroy proteins and cell membranes.

As light can only penetrate tissue to a depth of 10-20mm PDT compounds can only be activated to cause tissue damage within superficial lesions. As most photosensitisers depend on the presence of oxygen to produce their cytotoxic effect, an adequate blood flow to the treatment area is essential.

Fourteen patients with Barrett's mucosa, with or without dysplasia, received therapeutic treatment for the first time in 1993 [69]. In the largest reported series to date Overholt and Panjehpour, described their experience in 35 patients with high-grade dysplasia, 14 of who also had early adenocarcinoma [153]. Using dihematoporphyrin-ether, photodynamic ablation of dysplastic or malignant mucosa was followed by healing and conversion of 75-80% of treated Barrett's mucosa to normal squamous epithelium. Complete elimination of Barrett's epithelium was achieved in 10(28%) patients. The major complication was stricture formation which occurred in 60% of patients.

One of the attractions of PDT for the treatment of Barrett's oesophagus is its technical ease of delivery, and a complete Barrett's segment can be obliterated in one session. Unfortunately, there are some drawbacks. Dihematoporphyrinether is a first generation photosensitiser and induces a photosensitisation of the skin, so that phototoxic effects in skin areas exposed to light may occur in the first few weeks after treatment. Secondly, selective ablation of the dysplastic tissues cannot be reliably achieved without damaging deeper layers of muscular tissue resulting in oesophageal stricture formation.

In an attempt to reduce the complication rates of mucosal ablation using PDT, 5-aminolevulinic acid (5-ALA) has been used as the PDT agent in more recent studies. PDT with 5-ALA is unique because the photosensitiser (protoporphyrin IX (PpIX))

is synthesised in vivo after administration of a precursor compound. Exogenously administered 5-ALA results in the production of much greater levels of PpIX in the mucosa of the gastrointestinal tract than the submucosa and muscularis, making it an attractive agent for use in mucosal obliteration [154]. In addition, skin photosensitivity with 5-ALA lasts only a few days.

Considerable interest was been generated by a small pilot study reporting eradication of high grade dysplasia in columnar-lined epithelium by endoscopic photodynamic therapy using 5-ALA [155]. Patients were also treated with omeprazole 40mg daily and were followed up for 26 to 44 months. Gossner et al report a larger study of photodynamic therapy using 5-ALA in 10 patients with high grade dysplasia and 22 with carcinoma [156]. High grade dysplasia was eliminated in all 10 patients, and although large portions of the treated oesophagus were subsequently re-epithelialised, complete eradication of Barrett's epithelium was not seen. In two cases specialised columnar epithelium was found underlying newly formed squamous epithelium. Early cancers were only obliterated in 17 of the 22 patients. In particular lesions thicker than 2mm were not adequately treated by this method.

It seems that the optimum depth of penetration of PDT has not yet been achieved. Further controlled studies need to be performed before PDT can be recommended for routine treatment of Barrett's oesophagus.

1.10.2.2 Thermal laser therapy

Several studies have examined the ability a variety of endoscopic laser therapies to ablate Barrett's epithelium and permit re-epithelialisation with squamous epithelium. The different types of laser cause different depths of tissue penetration. The

estimated penetration of the Nd:YAG laser is 4mm whereas with Argon plasma coagulation it is 1mm [157].

A small study form Luman et al that randomly assigned eight patients with Barrett's epithelium to acid suppression with and without Nd:YAG laser photocoagulation found no change in the extent of Barrett's epithelium in both groups [158]. It is possible that the greater depth of tissue penetration with the Nd:YAG laser could have destroyed the multi-potential stem cells thought to be essential in allowing re-epithelialisation. Secondly the technique of laser therapy seems to be important. In this study, laser therapy was applied retrogradely, starting at the gastro-oesophageal junction and moving more proximally. Hence the ablated area remained surrounded by columnar epithelium. Berenson et al have suggested that the best response to laser therapy occurred when columnar epithelium was lying adjacent to squamous epithelium [159]. Sampliner et al reported regression of Barrett's epithelium after ablation with Nd: YAG laser and acid suppression in a 76-year old man [160].

Other unsuccessful results of laser photoablation of Barrett's epithelium have also been described. Brand and Kauvar reported that an initial endoscopic examination performed six weeks after treatment with Nd: YAG laser revealed no endoscopic or histologic signs of Barrett's epithelium, but follow-up endoscopic examination 14 weeks later showed that Barrett's epithelium had reappeared despite acid suppression with 20mg omeprazole daily [161].

One of the reasons for failure in these studies could be that medical therapy does not prevent the reflux of duodenal contents into the oesophagus. In order to prevent this, one study has examined the combined use of endoscopic laser ablation and anti-reflux surgery in 10 patients with Barrett's oesophagus [162]. One to eight treatments

with the Nd:YAG laser were required for all the intestinal metaplasia to be ablated and for squamous epithelium but no intestinal metaplasia to appear in the biopsies. Squamous reepithelialisation was complete in all but two patients in whom intestinal metaplasia persisted in the gastric cardia, and remained during a mean follow-up of 26 months. In a control group of six patients who had surgery alone, the length of intestinal metaplasia in biopsies at endoscopy remained unchanged during the mean follow-up period of 21 months.

Barham et al used the KTP laser in 16 patients with non-dysplastic Barrett's oesophagus all of whom were on acid suppressive therapy [156]. All laser treatments resulted in squamous regeneration confirmed endoscopically and histologically. The number of treatments required depended on the length of Barrett's segment. In 11 of the patients there was evidence of squamous regeneration over remaining Barrett's glands.

Several studies have reported encouraging results of the use of APC to ablate columnar-lined oesophagus and facilitate squamous re-epithelialisation. In one study, ten patients with Barrett's oesophagus received acid suppression and treatment with APC at 2-5 week intervals. During multiple endoscopic sessions, one to eight segments of Barrett's oesophagus ranging from 0.25cm^2 to four cm^2 were treated using APC until the treated segment turned white. Thirty-eight out of 40 treatment locations partially or completely re-epithelialised with squamous tissue. However, glandular tissue persisted beneath the squamous epithelium [159]. In a more recent study, 13 patients with Barrett's oesophagus were treated with the APC [163]. Some degree of replacement of Barrett's lining by squamous epithelium occurred in all patients. Success (macroscopic and histological regrowth of squamous epithelium

in>80% of the Barrett's oesophagus) was achieved in five patients. In these patients, there was no histological evidence of squamous epithelium overlying columnar epithelium.

Another study has suggested complete restoration of squamous mucosa in 70% of the 21 patients treated with APC in combination with a PPI [164]. Others have suggested that normalisation of oesophageal acid exposure is important in preventing recurrence of Barrett's oesophagus at one year follow-up. Martin et al treated 25 patients with Barrett's oesophagus with repeated APC and acid suppression [165]. They found that approximately one session of APC per one cm of Barrett's mucosa was needed.

Although such endoscopic therapies are promising, it is of concern that several studies have reported the occurrence of specialised columnar epithelium underlying newly formed squamous epithelium. This has occurred after photodynamic therapy [156], multipolar electrocoagulation [151], APC [159,166], and the KTP laser [167]. These observations have raised concerns that the treatment of Barrett's epithelium may be harmful in the long run if overlying squamous mucosa makes surveillance of Barrett's epithelium more difficult. Furthermore unless complete eradication of Barrett's epithelium can be reliably achieved there is still the possibility that dysplasia would occur at a later date.

The mechanism of reepithelialisation is unclear. Biddlestone et al have examined the histopathology of Barrett's oesophagus after treatment with acid suppression and laser and photodynamic therapy [168]. The histologic findings suggest three main mechanisms for reepithelialisation: encroachment of adjacent squamous epithelium at the squamo-columnar junction, extension of epithelium from the submucosal

gland duct to form squamous islands, and squamous metaplasia within the Barrett's columnar mucosa itself.

A further question that remains unanswered is whether cancer risk is actually reduced in the regenerated squamous epithelium. As yet no long term randomised study comparing untreated versus reversed Barrett's oesophagus patients has been reported. One recent study has looked at several cancer risk biomarkers to establish whether reversed squamous epithelium after multipolar electrocoagulation is biologically normal and poses a lower risk [169]. Using histology, ornithine decarboxylase activity, Ki-67, PCNA, and p53 mutations they confirmed that the reversed squamous epithelium was biologically similar to normal epithelium and hence may not be associated with increased cancer risk.

Even if endoscopic treatment of Barrett's proves effective, the impact of treatment on outcome still needs to be established.

CHAPTER 2- Oesophageal cancer (A critical review of the literature)

2.1 Epidemiology

Oesophageal cancer has an estimated incidence of about 7.5 per 100,000 in the UK and accounts for more than 3500 deaths per year [170]. The incidence of squamous cell carcinoma varies widely in different geographical areas. Areas of high incidence include NE Iran, N. Afghanistan, S. Russia and N. China. Non-Caucasian males are most commonly effected. Oesophageal adenocarcinoma is a disease of the Western male. Prior to the 1970's this was a rare disease but over the past three to four decades there even seems to have been a disturbing increase in the occurrence of oesophageal cancer in the UK, USA and Western Europe [86-88];[171].In the USA according to data from the Surveillance, Epidemiology, and End Results (SEER) program, this rate of increase exceeded that of any other type of cancer during the period 1970 to 1989[87]. Several methodological issues, including improved specification of diagnosis in terms of anatomic site and histologic type, were considered as possible confounding factors, but were felt unlikely to explain this trend [87];[172]. The reason for the increasing frequency of oesophageal adenocarcinoma is unclear.

2.2 Aetiology

Tobacco and alcohol abuse are associated with the development of squamous cell cancer, but not with adenocarcinoma [173];[174]. The major risk factor for the development of adenocarcinoma is the presence of the pre-malignant Barrett's

oesophagus which is thought to be a consequence of gastro-oesophageal reflux [33,175]. The degree of risk has been reported by several studies and varies from between 30-125 times the normal population [59-61,69,176-178]. One epidemiological study has examined the use of pharmaceutical agents which relax the lower oesophageal sphincter possibly resulting in gastro-oesophageal reflux and Barrett's oesophagus [179]. Between 1957 to 1986 in the USA there has been an upward trend in the use of such drugs purchased per capita through retail pharmacies and hospitals. This study makes a speculative association between the increased use of drugs relaxing the lower oesophageal sphincter and the rising incidence of oesophageal adenocarcinoma in the USA. Obviously this hypothesis needs to be tested in a case-control study.

There has also been speculation around the relationship between Helicobacter Pylori (HP), and the development of Barrett's oesophagus and oesophageal adenocarcinoma. Several studies which examined the prevalence of HP in both gastric and oesophageal specimens from patients with Barrett's oesophagus have been reviewed[180]. In a total of 360 patients, oesophageal colonisation was found in 23.2%. Gastric Helicobacter pylori colonisation was documented in 71% of cases. Of these 261 patients, 22% had gastric infection. This figure is similar to that expected in the general population and does not support a role for Helicobacter pylori in the pathogenesis of Barrett's oesophagus. Few studies have examined the role of HP in the progression from Barrett's oesophagus to adenocarcinoma. Quddus et al found no evidence of HP in 19 patients with adenocarcinoma arising in Barrett's oesophagus [181]. Henihan et al found a significant association between HP and severity of inflammation in patients with Barrett's oesophagus[182]. HP was

absent in patients with adenocarcinoma and moderate to severe dysplasia. Wright et al reported a negative correlation between HP and increasing dysplasia[183]. These results are very preliminary and further prospective studies are required to elucidate the role of HP in the development of oesophageal adenocarcinoma.

2.3 Palliative treatments for oesophageal cancer

The prognosis of this disease is extremely poor, with a median five-year survival of about 5% [184]. Only one third of patients are suitable for curative resection at presentation and for the remaining patients, only palliative therapy is possible. Effective palliation of dysphagia is the goal of treatment as this is the cause of much debility and distress. A variety of different techniques have been developed [185]. Conventional palliative procedures for advanced oesophageal cancer include surgery, radiotherapy, chemotherapy and surgical insertion of plastic prostheses [186]. More recently advances in both endoscopic and radiological techniques have enabled the development of less invasive methods of palliation, including laser therapy and insertion of expandable metal stents.

2.3.1 Surgery

Surgical relief of dysphagia can be achieved by resection. Although the best way of palliating dysphagia, such surgery is associated with a high morbidity, mortality and prolonged hospital stay. Mortality rates for bypass surgery vary from 20%-30% [187-190]. One study has reported a mortality of 11% with 82% of patients having a complete and lasting relief of dysphagia [191]. Surgery is not commonly used for palliative therapy as such figures make it difficult to justify its use in patients with

advanced disease who have a short life expectancy and often significant comorbid disease.

2.3.2 Radiotherapy

External beam radiotherapy (EBRT)

Radiotherapy, as compared to endoscopic therapies has the potential to inhibit local tumour growth. Radiation may be either given by external beam or through an intraluminal source (brachytherapy). About 50-70% of both squamous cell carcinomas and adenocarcinomas respond to EBRT[192-196]. However, the relief of dysphagia may take several weeks and the general debilitating effects following radiotherapy may detract from any improvement in swallowing. In addition complications such as fibrotic strictures and oesophago-respiratory fistula occur in about 30% of patients [192-196].

Brachytherapy

Intraluminal radiotherapy was made possible by the development of the Selectron remote control after-loading machine. The biggest advantage of brachytherapy is its ability to provide the highest dose of radiation to the tumour whilst sparing the normal tissues. It has proved to be a safe and effective method of palliation [197,198]. Fleischman et al reported 10 patients with advanced oesophageal cancer who underwent a short intensive course of intraluminal brachytherapy. Ninety % of the patients had improvement in their dysphagia with an average response of 5.1 months. The only complication was mild to moderate oesophagitis in about half of the patients one week after treatment [199].

Combined EBRT and Brachytherapy

The combination of brachytherapy with EBRT has achieved even better response rates, although troublesome oesophagitis can occur in up to 80% of cases [200-202]. Pakisch et al have reported the use of this approach in 48 patients who had either unresectable local tumours or who were medically unfit [203]. Patients underwent high dose rate brachytherapy followed by EBRT. Of the 41 who completed the treatment 21(71%) returned to a normal diet. All patients who received more than 50 Gy of EBRT suffered mild to moderated oesophagitis and late complications developed in 29%. In another study, 67 patients received EBRT followed by brachytherapy. Swallowing was restored in 92% of patients 4 weeks after treatment, although half required late dilatation for stricture formation [204]. In a study of 46 patients undergoing EBRT and brachytherapy, 76% received moderate to good palliation compared to 52% with EBRT alone [196]. In another study, 35 patients underwent EBRT followed by low-dose-rate brachytherapy [205]. At six weeks post-treatment, 90% of the group could eat solid food. Most patients were well palliated until 2-4 weeks prior to death. Severe oesophagitis requiring hospitalisation occurred in 14% of patients, and late complications developed in 17%. Although the combination of EBRT and brachytherapy looks promising, a randomised control trial of EBRT alone versus EBRT and brachytherapy is needed.

2.3.3 Chemotherapy

Chemotherapy has been used as an adjuvant therapy in several studies and as a single modality in two randomised trials [206;207]. In one non-randomised trial of 33 patients receiving palliative treatment for oesophageal cancer, 23 out of 30 patients

were dysphagia- free following chemotherapy [208]. Patients with distal thoracic tumours did significantly better than proximal and mid tumours [209]. This study reported a 56% rate of moderate to severe toxicity, and Herskovic reported a 64% rate of severe and life-threatening acute toxicity [206]. However, mortality was low (<2%) with few late complications. When used alone chemotherapy seems to have impressive survival figures [206], but this has to be balanced against prolonged treatment and significant morbidity in patients with poor life expectancy.

2.3.4 Dilatation

Dilatation is rarely used alone for the palliation of malignant dysphagia due to its short duration of effect, but it is often required to permit the delivery of other palliative techniques. Two studies have examined the use of dilation alone. In a study of 38 patients receiving dilation alone for palliation of malignant dysphagia, it was not possible to pass a guide wire in 15% of patients and 31% of patients had no benefit from the treatment [210]. The mean dysphagia free period was 11.5 days. The second study performed dilation at four weekly intervals in 41 patients [211]. They reported a good relief from dysphagia initially, but 22% of patients eventually required intubation. The main complications of oesophageal dilation are perforation, aspiration, and bleeding giving a complication rate of 2.5-10% [212].

2.3.5 Photodynamic Therapy

Photodynamic therapy has been used to palliate malignant dysphagia. McCaughan reported the use of PDT for palliation of oesophageal cancer in 40 patients [213]. At one month the mean luminal diameter had increased from 6mm to 9mm.

Complications were frequent and included stricture formation (15%), tracheo-esophageal fistula (7.5%), and localised third-degree burns (2.5%). It may be useful in patients with cervical strictures and can be applied to totally obstructing cancers [213;214]. PDT can be used repeatedly and in patients that have failed other modalities. Further evaluation of its efficacy is required.

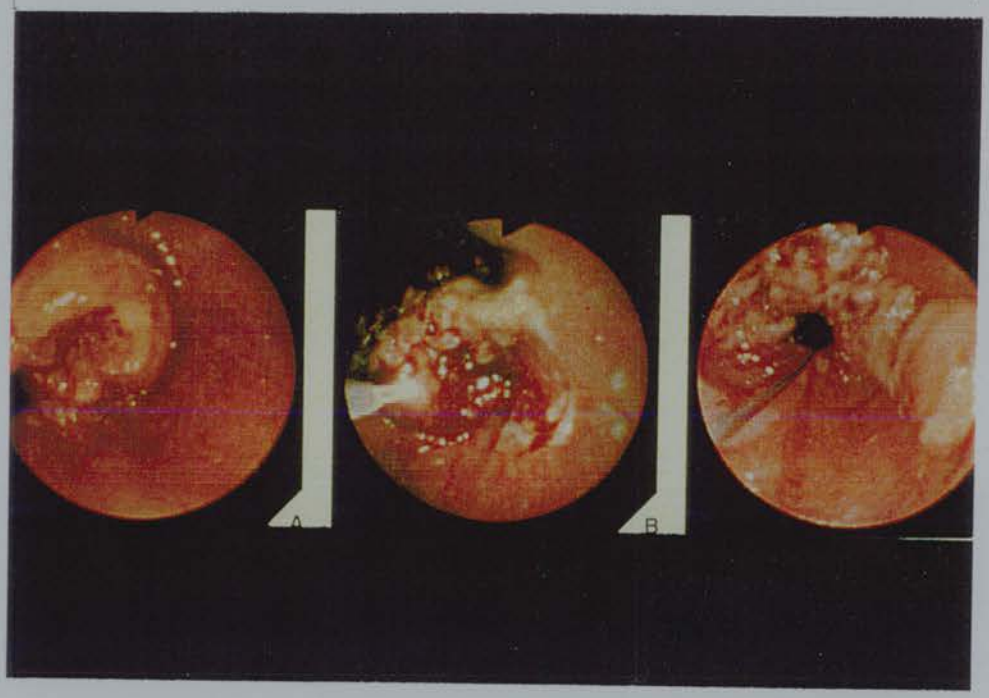
2.3.6 Laser Therapy

Endoscopic laser therapy for the palliation of oesophageal cancer was originally described be Fleischer, in 1982 [215]. This procedure can be performed in an outpatient setting under intravenous sedation. For tumour vaporisation, the Nd:YAG laser is usually applied in the non-contact mode using a high (70-150 watts) power settings at distance of 0.5-1cm from the tumour (Figure 2.1). The laser light is transmitted via a flexible quartz fibre which is enclosed within a Teflon sheath. This is passed down the biopsy channel of a standard flexible endoscope. Initial dilatation and retrograde approach technique are favoured to minimise complications [216]. Pre-treatment dilatation is required in 20% of patients with totally obstructing tumours to facilitate the passage of the endoscope into the stomach [216].

Luminal patency can be achieved in 90-100% of patients using the Nd: YAG laser. However, anorexia, general debility and pain contribute to a poor quality of life. Frequently quoted factors associated with a poor response to laser include tumour location in the upper third of the oesophagus or the gastroesophageal junction and the presence of a sub-mucosal tumour [217]. The response to laser has also been shown by some to decrease as stricture length increases [218], but others have not supported this [219].

Figure 2.1 Endoscopic Nd:YAG laser therapy to an oesophageal tumour

Endoscopic pictures from left to right: occluded oesophageal lumen; endoscopic laser therapy to oesophageal tumour; luminal patency restored.



The major early complications of laser therapy are oesophageal perforation, fistula formation, and haemorrhage. In a review of several series, the total perforation rate was 3%, bleeding rate was 1.4%, and fistula formation within two weeks of treatment was 2.3% [220]. Perforation generally results from pre-treatment dilatation and responds to conservative management in over 80% of cases. Haemorrhage can be controlled with local laser photocoagulation.

The major advantages of laser therapy are its high success rate with low risk of complications. An immediate improvement in dysphagia occurs and the treatment can be repeated indefinitely. However regrowth of tumour into the lumen often develops and in most series, repeated treatment is required at four to eight week intervals [175;221]. Thus, laser therapy is usually repeated on numerous occasions, particularly in long term survivors. In most studies the duration of palliation has not been well documented. Bourke et al evaluated dysphagia scores after treatment and within two weeks of death[217]. Although 96% of patients were palliated initially, only 73% were swallowing well at the later stage. Only half of patients maintained their initial level of palliation and 27% required stent placement. One study has even suggested that laser therapy is effective for prolonging survival in patients with squamous cell carcinoma of the oesophagus [222]. However this was a small retrospective study, so the results should be treated with caution.

In an attempt to increase the duration between laser treatments and to treat extraluminal disease, external radiotherapy and brachytherapy have been added. Laser plus brachytherapy provides good palliation and may provide a longer dysphagia free interval than historical controls treated with laser alone [223;224]. Shmueli et al evaluated a combination of Nd:YAG laser and intraluminal

radiotherapy in 32 patients with inoperable oesophageal carcinoma [224]. Patients with squamous cell carcinoma also received external radiotherapy. After treatment, all patients were able to ingest a semisolid diet, although 18 patients developed symptomatic fibrous strictures. Two thirds of patients eventually required some form of later endoscopic intervention. It is unclear whether the addition of brachytherapy reduced the need for repeated endoscopic intervention.

In another randomised trial 12 patients received either laser therapy alone or laser therapy followed by the insertion of an Oesophageal Wallstent. Swallowing was similar in both groups. The third of patients who had a short life expectancy did not benefit from the combined therapy. In the remaining patients the dysphagia free time was increased by a factor of two to four [225].

Although, the Nd: YAG laser has mainly been used for palliation of oesophageal cancer, in a recent study, 9 patients with malignant dysphagia were successfully palliated using APC [226]. This technique needs further evaluation.

Nd:YAG laser therapy has therefore been established as a safe an effective technique for palliating malignant dysphagia. However few trials have compared it with newer methods of palliation such as insertion of expandable metallic stent.

2.3.7 Intubation

2.3.7.1 Plastic Prosthesis

Endoscopic intubation is a well-established treatment for the palliation of malignant dysphagia. Initially, rigid plastic tubes were introduced at laparotomy, with a mortality as high as 45% [227;228]. Atkinson et al developed a technique for the endoscopic insertion of plastic prostheses with a reduced complication rate [229;230].

Although insertion of semi-rigid prostheses gives rapid relief of dysphagia, the quality of swallowing is often poor and most patients are unable to consume a normal diet after intubation [231]. This seems to occur because although the outer diameter of these tubes is relatively large, the inner lumen is relatively small. If all complications are considered, the reported morbidity ranges from 22%-60%[232-235]. Early complications include perforation (6%), haemorrhage (3.5%), aspiration pneumonia (0-2%) and tube dislocation (15%) [220;236]. Late complications include obstruction (9.5%), dislocation (8%), and pressure necrosis (3%). In a review of several series, hospital mortality averaged 8%[220].

Despite the associated morbidity, intubation has several advantages. It can be performed in a single session, hospital readmission may be unnecessary. Oesophageal fistula can be sealed.

2.3.7.2 Expandable Metallic Stents

In an attempt to reduce the complications of the standard prosthesis, a new class of expandable metallic stents has been developed. Frimberger first proposed their use in 1983 [237] (Figures 2.2, 2.3, 2.4). The theory is that an expandable metallic stent can be restrained within a much smaller delivery system, allowing safer introduction into the oesophagus and across the stricture. Removal of the restraining device enables the stent to expand to a large diameter, resulting in rapid palliation of dysphagia. A variety of different designs are available. The three most commonly used types are the Wallstent, the Ultraflex device and various modifications of the Gianturco stent.

The Wallstent is a self-expanding, metallic-mesh stent originally designed for use in the biliary tree. Two sizes of Wallstent are available: 20mm diameter and 110mm in length, on an 18F delivery system, or 25mm diameter and 105mm length on a 22F

delivery system. The middle 7cm is covered with polyurethane. The compressed stent is arranged within three coaxially arranged shafts. The system allows the distal 50% of the stent to be released before repositioning of the stent and full deployment. The Ultraflex mesh is an uncovered stent made of a knitted nickel-titanium alloy (nitinol), which has thermal memory characteristics. It has a diameter of 18mm when fully expanded and are available in three lengths (70,100 and 150mm).The proximal end of the stent is slightly flared to improve its anchoring to the oesophageal wall. It is compressed and encased in gelatine within a 24F plastic sheath. After placement the stent is released by retraction of the delivery sheath. Oesophageal fluids dissolve the gelatinous material, allowing the stent to expand.

Figure 2.2 Expandable metallic stent (Wallstent)

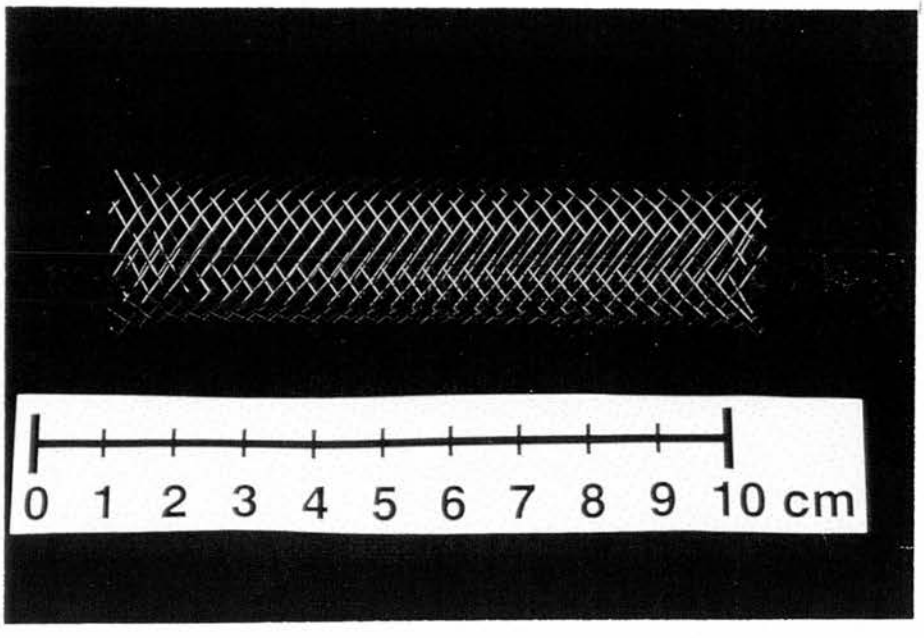


Figure 2.3 Radiologically placed expandable metallic stent

Under fluoroscopy, the stent can be seen well placed and expanded in the oesophagus

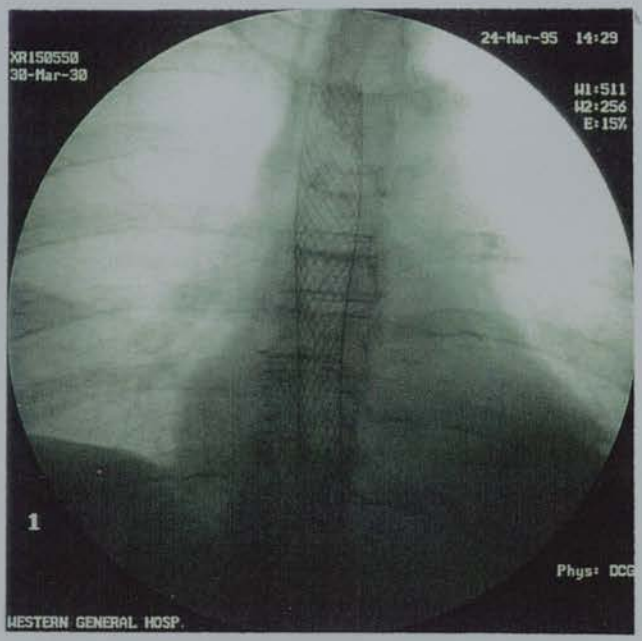


Figure 2.4 Endoscopic view of expandable metallic stent.

The stent has expanded well providing a clear lumen within the oesophagus

The Gianturco stent is constructed from a basic unit in which a 0.018-inch stainless steel wire is bent in a zigzag fashion to form 2cm long segments. Multiple segments are then sutured together to form the prostheses. The stent is covered in polyethylene to prevent tumour ingrowth. Hooks on the external surface of the central bodies prevent stent migration.

The first successful use of a metallic stent in oesophageal carcinoma was reported by Domschke et al in 1990 [238]. Since then there have been many reports of their use, some with long-term results. Most of these studies have been uncontrolled and are summarised in Table 2.1. Most series report good palliation of dysphagia but also highlight problems and limitations. In one uncontrolled study, 26 patients received uncoated Nitinol stents [239]. In one patient a broken stent strut caused a partial stenosis, whilst three others had recurrent dysphagia due to tumour in-or overgrowth. A second similar study in 59 patients revealed tumour in- or overgrowth in 21(36%). 51% of patients required further intervention.

One of the earliest controlled trials compared the insertion of an uncoated metal stent and a semi-rigid endoprosthesis in 42 patients with malignant dysphagia [240]. Although the dysphagia scores improved significantly and similarly in both groups, there was a significantly higher rate of complications with the plastic prostheses, including three deaths, and a longer duration of hospital stay. The recurrent dysphagia rates were similar, with the plastic prostheses prone to migration, whilst the metal stents were occluded either by tumour overgrowth or ingrowth. Similarly, De Palma et al have performed a randomised trial directly comparing conventional plastic prostheses versus expandable metal stents [241]. Rates of successful stent placement and improvement in dysphagia scores were similar in both groups, but

expandable stents had a significantly lower complication rate (0% vs 21%) and procedure -related mortality (0% vs 15.8%). This is a particularly high mortality and complication rate in the plastic stent group and may have been related to vigorous dilatation prior to stent placement.

In a retrospective study, 38 patients who received expandable metal stents were compared with 47 patients who received plastic stents [242]. Insertion complications, procedure-related mortality, and improvement of dysphagia were similar in both groups. However subacute complications such as chest pain, stent migration, stent occlusion, stent erosion and aspiration pneumonia, were found to be higher in patients receiving expandable stents (80%) as compared with those receiving plastic stents (60%).

In a recent randomised prospective study, 75 patients were treated with either a Celestin tube or an uncoated Gianturco stent [243]. Again, major complications were significantly less frequent in those receiving the expandable metal stent. Previous radiotherapy or chemotherapy predisposed to more device related injury. A second randomised study compared the use of the Atkinson tube and the Gianturco stent for the palliation of 31 patients with inoperable oesophageal carcinoma [244]. In this study, quality of life was assessed using the Nottingham Health Profile. This showed that patients treated with Gianturco stents maintain their weight for longer, with improved swallowing, appetite and quality of life when compared to those with Atkinson tubes.

Table 2.1(1) Summary of studies examining the use of expandable metallic stents

Author and year	Number of patients	Type of stent	Successful placement	Improvement in dysphagia	Complications	Stent related mortality
1.ELL1995 [245]	20	GIANTURCO-Z STENT	100%	MEDIAN SCORE FROM 2.1 TO 0.5	2-STENT MIGRATION 1-STENT OVERGROWTH	NIL
2.Nicholson 1995 [246]	12(11 oesophageal perforation)	9-covered Cook 3-covered Wallstent	100%	All improved	2-Stent overgrowth	
3.Moores 1996[247]	20-5 Benign stricture	Covered Wallstent	100%	All able to eat solid foods	1-Stent migration	5%(Bronchoesophageal fistula)
4.Acunas 1996[248]	59	Nitinol-Boston Scientific	100%	At least 1 grade in all but one patient	36%-stent overgrowth/ ingrowth 5%-fistula 7%-ulceration 5%-stent torsion	NIL
5.Feins 1996[249]	13	Covered Wallstent	100%	12/13 improved	1-stent migration 1-stent overgrowth	NIL
6.Pocek1996 [250]	27	Streker stent	100%	Mean Score from 2.3 to 1.0	4- stent overgrowth	1 patient due to IHD
7.Grund 1995 [251]	114	Ultraflex stent	97%	Mean Score from 3.5 to 1.5	66%-tumour ingrowth	NIL
8.Winkelbauer 1996 [239]	26	Nitinol-Boston Scientific	25/26- 1 broken strut		2- tumour overgrowth or ingrowth	NIL

Table 2.1(2) Summary of studies examining the use of expandable metallic stents

Author and year	Number of patients	Type of stent	Successful placement	Improvement in dysphagia	Complications	Stent related mortality
9.Ellul 1996 [252]	130 185 stents	91-covered,1-uncovered Wallstent 6-covered Gianturco stent	100%	Mean Score from 3 to1	Total=42% 19-stent migration(18 GO Junction) 18-tumour overgrowth/ingrowth 4- food bolus	1-IHD 1-GI Bleeding
10.May 1996 [253]	87 96 stents	A. 31 Wallstent (5 covered) B. 35- Ultraflex C. 30 Covered Gianturco Z-stent	100%	Mean Score from..to. A. 2.0to0.7 B. 2.2 to 0.9 C. 2.1 to 0.7	Rate of complications A. 48% B. 44% C. 26%	Nil
11. Schmassmann 1997 [254]	82	A. 44 Uncovered Wallstent B. 38 Nitinol Stent	100%	Median Score from 3 to 1	Early A. 32% B. 8% Reintervention A. 9% B.34%	A.16% B.0%
12.Bethge1996 [255]	17	Uncovered Wallstent	100%	At least 1 point 13/17- 2 points	3 patients	1-Bleeding 2-sepsis
13.De Palma 1995 [256]	32	Ultraflex	94%	Mean dysphagia score from 3.0 to 0.5	3-food bolus impaction 3- tumour ingrowth 1- tumour overgrowth	Nil
14.May 1995 [257]	30	Ultraflex	100%	25/30 improvement	1-perforation 9-tumour ingrowth/overgrowth	Nil

Table 2.1(3) Summary of studies examining the use of expandable metal stents

Author and year	Number of patients	Type of stent	Successful placement	Improvement in dysphagia	Complications	Stent related mortality
15.Miyayama 1995[258]	27	Covered Gianturco stent	100%	7%-liquids only 37%-soft diet 56%-solid food	4%- new stricture 7%- new fistula 15%- stent migration	Nil
16. Watkinson 1995[259]	32	Wallstent	100%	Median score from 3.38 to 0.8	11 further stents- Migration, tumour ingrowth, or long stricture	Nil
17.Wagner 1994[260]	18	Nitinol	100%	Mean score from 2.7 to 0.6.	???	Nil
18.Neuhaus 1992[261]	10	Wallstent	100%	Mean score from 2.9 to 2.0	1-perforation 2-food impaction 2-tumour ingrowth	Nil
19.Schaer 1992[262]	6	Z-stent	100%	Score decreased by two grades	1-stent migration 1-tumour ingrowth 1-food impaction 1-perforation	Nil
20. Cwikiel 1993[263]	40	Nitinol	100%	All improved	2-tumour bleeding 8-tumour ingrowth	Nil
21.Saxon 1995[264]	52	Gianturco Z-stent	100%	50/52 improved	5- migration, 2-impaction 1-tumour ingrowth 1-perforation 4-haemorrhage	4 patients
22.Wu 1994[225]	32	Gianturco Z-stent	100%	mean score from 3.21 to 1.08	4migration,2impaction, 1sepsis,2-in-or over-growth	1-haemorrhage

2.3.8 Comparison of treatments

Cwikiel has made a comparison of the palliative effects on dysphagia of radiotherapy, chemotherapy and insertion of an oesophageal stent [265]. On completion of treatment 56% of patients treated with radiotherapy, 49% of those treated with chemotherapy, and 81% of patients treated with self-expanding metallic stent were free from dysphagia.

The most frequent comparison of endoscopic means of palliating malignant dysphagia has been that of laser therapy versus intubation. Two retrospective studies have shown that adequate palliation was achieved with a high success rate by both laser therapy and stent placement [266;267]. Several prospective studies have been performed. In one, 40 patients with malignant dysphagia were randomised to either endoscopic intubation or laser recanulisation[268]. The best swallowing grade achieved was significantly better with laser recanulisation (median 4) than with intubation (median 3). This better palliation in the laser group was not reflected in a significant improvement in survival. In a second non-randomised prospective study, 43 patients treated with the Nd: YAG laser were compared with 30 patients treated by endoscopic intubation [231] Initially patients with thoracic tumours responded equally to either method, although those with cardia tumours were better palliated by intubation. In patients palliated over a long period, the mean dysphagia grade for the remainder of their lives was better in the laser group. The perforation rate was lower in the laser group, but no treatment-related deaths occurred in either group.
One randomised study comparing laser therapy with self -expandable metallic stents [269]. In this 60 patients were treated with either covered stents (23 patients), or

uncovered stents (19 patients), or by laser (18 patients). Both stented groups had an improvement in dysphagia score by two points, whereas the laser group only improved by one point. Six of the covered stents migrated compared with none in the uncovered group, whereas the latter group had 26% tumour ingrowth. They concluded that both types of stent had a similar efficacy but they were better than laser therapy in palliating dysphagia. However, no data were collected regarding quality of life.

2.3.9 Survival

Although, the main aims of palliative therapy for patients with oesophageal cancer are improvement of dysphagia and quality of life, survival is an important consideration. Many studies do not present their survival data; the others are summarised in Table 2.2. In the studies comparing the use of the plastic stent with that of the expandable metallic stent, the latter group had a tendency to live longer [240;242;243;256]. Similarly, comparing laser therapy with the use of the plastic stent, laser treated patients had a better survival [231;268;270] There are very limited data for the comparison of laser therapy with expandable metallic stent. In the study by Adam et al, comparing laser therapy with both uncovered and covered stents survival was similar in all groups [269]. In another, smaller study laser treated patients had a significant survival advantage over stented patients [271].

Table 2.2 Comparison of survival in studies palliating oesophageal cancer

Author	Laser therapy	Plastic tube	Metallic stent
Carter 1992 [268]	Median 21.5(4-62) weeks	Median 14.5 (7-102) weeks	
Bourke 1996 [219]	Median 22(4-5)weeks		
Karlin 1987 [222]	Median 75.8weeks		
Spencer 1996 [223]	+brachytherapy Median 36(5-132) weeks		
Shmueli 1992 [221]	Mean 50(SEM 5) weeks		
Barr 1990[270]	Mean 18.3 weeks	+Laser Mean 16.1 weeks	
Acunas 1993 [248]			Mean 14 (1-56) weeks
Adam 1997 [269]	Median 8(1-29) weeks		Uncovered Mean 8.6 (1-43)weeks Covered Mean 6.8(1-28.5) weeks
Loizou 91 [231]	Mean 26 weeks	Mean 22.1 weeks	
Freitas 95 [272]	Mean 30 weeks (2-53)		
Maciel 96 [273]	Mean 20 weeks		
Robertson 1997 [226]	Argon Beam Median 14 (4-38) weeks		
Feins 1996 [249]			Mean:Alive 16(4.6-37.6)weeks,Dead7.7(2-20.6) weeks
Pocek 1996 [250]			Alive Mean 35.9(17.3-65) weeks Dead Mean 24.3 (0-56) weeks
Winklebauer1996 [239]			Alive Mean 60weeks, Dead Mean 22 weeks
May 1996 [253]			Median:Wallstent 12.7 (1-135) weeks,Ultraflex 15.3 (1-85.6) weeks, Gianturco 9.7 (1-42.8) weeks
Kynrim 1993 [240]		Mean 20.8 ± 4.14 weeks	Mean 23.9 ±4 weeks in those surviving 4 weeks
de Palma 1995 [256]		Median 26.8 weeks	Median 28.6 weeks
Kozarek 1996 [242]		Mean 12.4 (SD 10.3) weeks	Mean 12.8(SD 11.4) weeks
Siersema 1997 [243]		Median 11.6 weeks	Median 9.8 weeks
Saxon 1995 [264]			Dead Mean 11.7 weeks
Ell 1995[245]			Median:Alive 25 (12-39) weeks,Dead 9 (1-43) weeks

2.4 Health related quality of life (HRQOL) in patients with oesophageal cancer.

Carcinoma of the oesophagus frequently presents at an advanced or disseminated stage. Only about one third of patients present with resectable disease. For the rest, palliative procedures may be undertaken. The 'best' palliative treatment depends on the main aim of therapy. Relief of dysphagia and Quality of Life are now recognised as the most important aims in the palliation of malignant dysphagia.

2.4.1 Health Related Quality of Life (HRQOL)

Quality of Life (QOL) is a vague term and means different things to different people. HRQOL has developed out of recognition that only part of QOL is a consequence of health status, but in individuals with chronic disease, ill health is a significant contributor to QOL.

HRQOL is a difficult concept to define. One definition is 'The functional impact of an illness, and its consequent therapy, upon the patient, as perceived by the patient' [274]. There is no consensus as to what should be measured, and the literature includes a whole range of components that could be considered. Spilker identifies four major areas: physical status and functional abilities, psychological status and well being, social interactions, and economic status [275]. Physical status relates to a persons ability to carry out activities of daily living, whilst the psychosocial aspects deal with the effects of illness upon emotion and the social interaction with friends, family, colleagues and the community. Spitzer emphasised that some psychosocial

elements are more important that physical symptoms in patients suffering from chronic disease [276]. Ware has also suggested five inherent dimensions in HRQOL. These are physical health, mental health, social functioning, role functioning and general well-being [277].

2.4.2 Requirements of measures

All HRQOL tools must undergo rigorous assessment before they are accepted as valid tools for the measurement of disease outcome

Reliability

All instruments must produce the same results when used again under the same conditions.

The test-retest reliability can be examined, although in practice it may be difficult to distinguish measurement error from real changes in quality of life. Internal reliability, the extent to which items addressing similar concepts agree, should also be assessed. Inter-observer reliability also needs to be established.

Validity

The validity of HRQOL measures is more difficult to assess because HRQOL is by definition subjective. A crude approach is to examine face validity by asking a variety of people whether the instruments seem to cover the full range of topics. A more formal approach is to examine construct validity. This relates the HRQOL instrument with other more established measures. This may require examination of the instrument's ability to distinguish between patient groups considered to have different health status [278]. Once validity has been shown for one purpose it cannot be assumed for all possible populations or applications.

Sensitivity to Change

Although a HRQOL measure may be able to distinguish between patients at one point in time, they are not necessarily as sensitive to changes in patients over time when repeated. There are several reasons why HRQOL measures may be insensitive to changes over time. Generic questionnaires may be insensitive to change if they include several items that are irrelevant to the particular disease. Instruments may include items that are static, for example patterns of social relationships. If individuals score the minimum or maximum on a particular scale it will not be able to detect either further deterioration or improvement respectively. Lastly, the breadth of the categories may be too large to be sensitive to subtle changes in patients.

Appropriateness

To ensure that the quality of life measure used is the most appropriate, the health problem and likely impact of treatments being investigated need to be carefully considered.

Practicality

For routine use, the more detailed and comprehensive HRQOL questionnaires are both impractical to administer and hard to process and interpret. Briefer questionnaires may mean that important information about patients' experiences is missed and the validity and responsiveness of shorter instruments need to be studied.

Who should measure HRQOL?

HRQOL as assessed by the patient provides a more subjective view, whereas if assessed by a health professional a more objective view may be obtained. There is much controversy as to whom the best person to measure HRQOL is. Slevin et al have shown wide discrepancies between doctors' and patients' ratings of outcome in

relation to many medical therapies [279];[280]. They argued against observer assessment of another person's QOL because an individual's values and opinions cannot be assumed. Blazeby et al have shown poor correlation between proxy (both carer and health professional) and patient ratings of quality of life in patients with oesophageal cancer [281].

2.4.3 Types of HRQOL measurement

Quality of life instruments are generic or specific.

2.4.3.1 Generic instruments

These are a broad measure of health status and can be applied to a variety of populations. These tools can be further subdivided into health profiles or utility measures. The former examines various aspects of quality of life to which a score is given. The Sickness Impact profile is such an example, and assesses the impact of illness on daily activities and behaviour [282]. The advantage of such instruments is their ability to make health status comparisons both among patients with the same condition and between patients with different conditions. However, they may be too broad and fail to focus on important aspects of QOL in a particular population. Utility ratings have been designed by economists in an attempt to assign a numerical value to a health state. The most well known application of these is the quality-adjusted life year [283].

There have been many attempts to develop a generic questionnaire that is easy to administer, short, acceptable to patients, and has been fully validated.

The Sickness Impact Profile (SIP)/Functional Limitations Profile (FLP)

The SIP assesses the impact of sickness on daily activities and behaviour, rather than feelings and clinical reports. It consists of 136 questions not only on functioning but also on feelings of emotional well being and social functioning. The advantages of the SIP are that it can be either self-administered or interview based and it can be used with chronically or acutely ill patients. It has been well tested for reliability and validity [284,285]. Its limitations are its length and it can only be used with people who regard themselves as ill. Its responsiveness to change has not been demonstrated. The SIP has been adapted for use in the UK as the FLP, which however requires far more testing for reliability and validity.

The Nottingham health Profile (NHP)

The NHP was developed in the UK and is based on lay perceptions of health status. It was developed after interviews with a large number of lay people about the effects of illness on behaviour. The NHP relates to how people feel when they are experiencing various degrees of ill health. It was not intended to measure HRQOL but is useful as a survey tool for measuring perceived health. It is designed to be self-completed, contains 38 items and requires only a few minutes to complete [286]. It has been widely used to evaluate the outcomes of many therapies. It has been well tested for validity but only partly tested for reliability and sensitivity to change. However it has been criticised for being insensitive in its detection of low levels of morbidity that are important both clinically and to the patients [287].

Short Form 36(SF36)

The SF 36 was developed at the Rand Corporation in the USA for use in the Health Insurance Study Experiment/Medical Outcomes Study (HIS/MOS)[288]. It is a short questionnaire with 36 items within eight health scales to measure three aspects of health- functional status, well being, and 'overall evaluation of health'. The UK version of the SF-36 has been slightly modified from the original US version. The validity and reliability of the SF36 had originally been confirmed in the United States [289]. Further studies on large UK populations have confirmed it to be acceptable to patients, internally consistent, and a valid measure of the health status of a wide range of patients [290;291]. However, Garrett et al also recommend that it be used alongside a more disease specific questionnaire in order to measure many aspects of patient outcome. Ware et al reviewed the testing of the SF36 and found that it had a good validity and was more sensitive to changes in health than the NHP [292]. The SF-36 was able to discriminate between groups with differing degrees of physical disability. They also reported the results of a factor analysis, which provided strong evidence for the conceptualisation of health underlying the SF36.

The length of the SIP precludes its use in patients with oesophageal cancer and the NHP is relatively insensitive at low levels of morbidity. The SF36 provides a good measure of health status amongst a wide range of patients and was chosen as the most appropriate generic test for measurement of HRQOL in patients with oesophageal cancer.

2.4.3.2 Disease specific instruments in Oesophageal Cancer

These are designed for specific populations or conditions and focus on particular areas relevant to the group. Such questions are more understandable to the clinician, but cannot be applied in other settings.

The measurement of quality of life in patients with oesophageal cancer has been a neglected area. A recent review using Medline identified only 51 of 7569 references on oesophageal neoplasm that considered quality of life [293]. Of these only three used documented QOL instruments with appropriate statistical testing [270;294;295]. Most of the other studies used a dysphagia score as a measure of QOL with or without a simple measure of performance status. The study concluded that there was currently (1994) no well validated instrument for measurement of QOL in patients with oesophageal carcinoma.

Carcinoma of the oesophagus often presents with dysphagia, and swallowing difficulty is one of the most distressing and debilitating symptoms for the rest of the patients' life. Although the majority of studies assessing palliative therapies have not included a measure of quality of life, most have included a dysphagia score. However, it seems that improvement in dysphagia does not necessarily correlate with an improvement in quality of life. One study was specifically designed to measure quality of life in 59 patients following treatment for oesophageal carcinoma using the EORTC QLQ-C30 questionnaire [296]. This showed no correlation between dysphagia grade and various scales of QOL.

Other studies have achieved different conclusions. Loizou et al compared the effect of laser therapy and endoscopic intubation on the palliation of malignant dysphagia

[294]. Two quality of life measurements were used, the Quality of Life Index and a Linear Analogue Self-Assessment. Although there was poor compliance with the questionnaires (52%), they reported a significant correlation between dysphagia score and both quality of life scales. They also found that although the palliative treatments initially resulted in an improved quality of life, this worsened appreciably as the patient's condition deteriorated during the terminal phase of disease. One of the main reasons for poor compliance was given as comprehension difficulties and the significant time required completing both questionnaires. In another study, Barr et al randomised patients with advanced disease to receive laser therapy only or initial laser therapy followed by endoscopic intubation [270]. The same Quality of Life measurements as Loizou et al were used. Spearman's rank correlation between these measurements and the results of a daily dysphagia diary kept by the patients were significant at the 0.005 value, but they were modest in magnitude; 0.27 with the Linear Analogue Scale and 0.43 with the Quality of Life Index.

O'Hanlon et al have examined Quality of Life in 69 patients undergoing treatment for oesophageal cancer using the Rotterdam Symptom Checklist, a dysphagia score and an activities of daily living questionnaire to assess the impact of therapeutic intervention to changing quality of life [297]. They showed that these instruments were able to discriminate between patients undergoing surgery and those undergoing palliative therapy at presentation. Both groups reported an improvement in dysphagia scores following therapy, whereas there was only an improvement in two parameters of the daily living questionnaire in the surgical group and in no parameter in the palliative group.

Several cancer specific instruments have been developed. One of the oldest instruments is the Karnofsky Performance Scale, which measures physical performance and dependency [298]. It was originally designed to assess palliative treatments for patients with lung cancer and consists of a simple scale from 1 to 100. Although easy to administer this scale is fundamentally flawed in being physician assessed and by not measuring the broader aspects of quality of life such as social and emotional well-being [299-301].

Spitzer's Quality of Life Index (QL) was developed for use by physicians in relation to cancer and chronically ill patients [302]. Prior to its development Spitzer et al attempted to identify the components of quality of life by questioning lay people as well as health professionals. This resulted in the inclusion of five dimensions in the final questionnaire: activities of daily living, occupation, perception of health, support, and outlook on life. Again this is a physician administered questionnaire and suffers from a lack of correlation with patients' scores [303]. It has also been criticised for its failure to sample adequately different dimensions of quality of life relevant to clinical trials [304].

The Functional Living Index-Cancer (FLIC) was designed for use on a wide variety of cancer patients [305]. This is self-administered and well-validated, but is long and lacks adequate specificity for clinical trials.

A number of specific instruments are relevant to patients with oesophageal cancer. Patients undergoing gastric surgery, particularly for peptic ulcer disease have been assessed using the Visick Scale [306]. However, this is physician administered and may be too subjective to represent the patient's true feelings. Also, as it has not been designed or validated for use with oesophageal cancer patients, it may miss areas of

concern. Another scale has been developed to examine quality of life after surgery for gastric cancer [307]. This correlates well with both the Visick and Quality of Life Index of Spitzer.

The European Organisation of Research on Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ) is a generic instrument designed for international clinical oncology trials [308]. It is a modular system that is self-administered. The basic questionnaire considers physical concerns, functional ability, emotional and family well being, treatment satisfaction, and social and occupational functioning. Its use in patients with a variety of different cancers has been reported [309];[310]. More recently the use of the core questionnaire has been assessed in oesophageal cancer patients [296]. The findings from this study led to the development of the oesophageal module (OES-24) to be used in addition to the core questionnaire [311]. This includes a dysphagia score and other quality of life questions specifically related to patients with oesophageal cancer. It aims to improve the detection of even small differences between different therapies.

2.4.3.3 Measures of psychological well-being

Several scales of psychological well being, particularly those designed to diagnose the common psychiatric conditions of anxiety and depression have been developed. To assess psychological morbidity in patients with physical diseases self-reported feelings of anxiety and depression and behaviour are used.

The Hamilton Depression Scale (HDS)

This is a widely used scale, which assesses both cognitive and behavioural components of depression, particularly through somatic aspects [312]. This scale

cannot be used to make a diagnosis of depression, but can be used to measure severity once the diagnosis has been made. It has good validity and reliability. Although this scale is popular, its reliance on measurement of somatic problems could cause confusion when used in individuals with physical disease.

The Beck Depression Inventory (BDI)

This scale was designed by Beck et al in 1961 specifically to examine depression [313]. Like the HDS it can only be used to assess the severity of depression once the diagnosis has been made. It was developed by measuring attitudes and symptoms in two groups of depressed patients who were undergoing psychotherapy. Several studies have reported its validity and reliability, although most of the testing has been carried out on psychiatric patients rather than those with physical illness. Beck et al published a comprehensive review of the literature on the reliability and validity of the scale [314]. This review also shows the scale to correlate well with the HDS and discriminate between depression and anxiety.

The Symptoms of Anxiety and Depression Scale (SAD)

SAD was developed in 1976 and assesses anxiety and depression by concentrating on recent symptoms [315]. This scale has been developed mainly for use in the elderly. Little work has been published regarding its validity and reliability, and Bowling suggests that far more work is required before it can be generally recommended [316].

Hospital Anxiety and Depression Scale (HAD)

The HAD Scale was developed to detect states of anxiety and depression within a hospital setting [317]. Its aim was to design a scale to measure mood without interference from physical illness and one to distinguish anxiety form depression. The HAD scale consists of 14 items on two scales. Individual items are scored from

0-3, the higher scores indicating more psychological distress. HAD depression ratings of 7 or less were considered to be non-cases; scores of 8-10 were considered doubtful cases and scores of 11+, definite cases.

The authors purposely excluded all items related to both emotional and physical disorder, and questions were based solely on the psychological symptoms of neurosis. Question eight 'I feel as if I am slowed down' can be criticised for being unable to make this distinction between mood and physical health. Scores were not affected by the presence of physical illness, making the HAD scale attractive for clinical research. Although the authors present it as a valid and reliable instrument, Bowling indicates that this was only on the basis of 100 patients and suggests that much more work must be carried out before its performance can be judged [316].

None of these scales have been used to measure psychological and psychiatric morbidity in patients with oesophageal cancer. The HDS is unsuitable for use in this population due to the high number of items measuring somatic problems. The BDI although it has a high reliability has been used mainly in psychiatric populations. Although the majority of patients with oesophageal cancer are elderly, the SAD questionnaire still lacks good validity and reliability testing. Although the HAD scale also requires further testing, it seems the most appropriate tool to use in a group of patients with oesophageal cancer.

PART TWO: THE STUDIES

CHAPTER THREE-Treatment of Barrett's oesophagus

3.1 Introduction

As stated in chapter one, carcinogenesis in Barrett's oesophagus proceeds through a series of genetic alterations that activate oncogenes and disable tumour -suppressor genes. Proliferation associated antigens Ki67 and PCNA are increased in the columnar-cell lined oesophagus; [113];[131] and DNA content flow cytometry has shown that neoplastic progression is associated with cell cycle abnormalities [66]. The evolution from a normal cell to a malignant cell is frequently associated with a process of genetic instability that produces large changes in the DNA content (ploidy) of the cell. In addition, allelic deletions of multiple tumour suppressor genes have been demonstrated [138];[139]. Of these, TP53 gene mutations and p53 protein over-expression are early events in the malignant transformation.

Both medical and surgical therapy designed to reduce acid reflux have been reported to reduce regression of Barrett's epithelium, but as stated in chapter one, reports have been infrequent and controversial [145];[148]. Considerable interest has been generated by a small study reporting eradication of high grade dysplasia in columnar-lined epithelium by endoscopic photodynamic therapy using pulsed dye laser and a photosensitising agent [155]. Laser equipment is expensive; endoscopic APC is a new technology offering safe tissue ablation at a much lower cost. The equipment combines argon gas with a monopolar power source. The electrode in the

argon channel of the applicator is connected to an electrosurgical generator. The applicator ionises the argon gas where it remains ionised approximately 2-10mm distal to the tip of the applicator. Ionised Argon gas is electrically conductive. This allows the current to flow between the applicator and the tissue. Current density upon arrival at the tissue surface causes coagulation. The application of the energy to the tissue surface is uniform and contact free. No photosensitiser is needed.

Two studies have reported encouraging results of the use of APC to ablate columnar-lined oesophagus and facilitate squamous re-epithelisation [159;163]. No study however has addressed the question of whether the multistep neoplastic progression is halted by ablation therapy, or whether temporary regenerating squamous epithelium simply covers rather than replaces the metaplastic epithelium.

This study examines the ability of APC to reverse Barrett's oesophagus and to assess if this is associated with improvement in DNA aneuploidy, normalisation of cell cycle and abolition of p53 protein immunostaining.

3.2 Methods

3.2.1 Patient details

Patients identified with Barrett's oesophagus at routine endoscopy were considered for this study. Each patient had columnar-lined oesophagus with specialised intestinal metaplasia extending at least 2cm above the gastro-oesophageal junction. Patients gave informed consent. They were excluded if they had an oesophageal stricture or ulcer, were unwilling to take a proton pump inhibitor, had cardiovascular morbidity, taking anticoagulants or if they were female patients of reproductive age not using contraception.

3.2.2 Intervention

All patients were commenced or continued on a high dose of a proton-pump inhibitor (either omeprazole 40mg or lanzoprazole 30mg daily).

Endoscopy was undertaken under intravenous midazolam (2-7.5mg, Roche Ltd) and pethidine_(25-75mg) sedation. At initial endoscopy the upper border of the columnar-lined epithelium was defined and tattooed with India ink. Two mls of India ink were injected into the mucosa using a standard 23 Gauge injection needle (Variject, Microvasive, Boston Scientific Corporation) at 12 O'clock at the squamo-columnar junction with the endoscope in neutral and the buttons forward (Figure 3.1). Two photographs were taken of the oesophagus, using the same magnification each time. In the case of circumferential Barrett's, quadrantic biopsies were taken from proximal, mid and distal columnar lined epithelium using keymed 37K biopsy forceps (Keymed Ltd, Southend on Sea, UK). These biopsies were stored in formalin and sections were taken for histology and p53 immunostaining. Three biopsies from the mid level of each half of the oesophagus were taken and stored in tin foil at -20^0 c for flow cytometry analysis.

For circumferential Barrett's half of the columnar epithelium was then treated with APC (APC 300 ERBE, Eleckromedizin GmbH, Tubingen). The applicator was passed down the biopsy channel of the endoscope and the APC set on 50W. Coagulation treatment was commenced at the squamo-columnar junction (proximal). The aim was to ablate this junction and to create an appearance of closely spaced 'burnt white spots' (Figure 3.2). The half not treated served as an internal control to assess the effects of acid suppression. This internal control was selected to limit the number of patients in the study and to obviate matching variables.

Figure 3.1 Tattooing of the oesophagus with India Ink

Endoscopic picture showing blue staining of the oesophagus at 12 o'clock at the squamo-columnar junction.

Figure 3.2 APC treatment to half the oesophagus in Barrett's oesophagus

Closely spaced burnt white spots are observed covering the mucosa of the right half of the oesophagus.

3.2.3 Follow-up

Re-endoscopy was carried out at two and six months. Patients were asked about their symptoms of heartburn and dysphagia the week prior to endoscopy. At each of these endoscopies further photographs and multiple biopsies were taken as previously described.

3.2.4 Histopathology

All biopsies were examined by a single pathologist (Dr M MacIntyre) who was blinded to the labelling of the biopsies and to the side of the oesophagus treated with argon-beam coagulation.

3.2.5 p53 Immunohistochemistry

3.2.5.1 Principal of method

Non-specific antibody interaction is blocked by treating the sections with diluted normal serum of the host producing the secondary antibody. Monoclonal antibody against p53 is then placed into contact with the tissue and allowed to react. Secondary antibody, which is directed against the bound monoclonal antibody, is then placed on the tissue section and allowed to react. Finally Streptavidin-Biotin Peroxidase is added and this binds to the biotinylated secondary antibody. The process is then visualised histochemically by the reaction of peroxidase with its substrate, diaminobenzidene.

3.2.5.2 Apparatus

1. Square glass dishes

2.Funnel and filter paper (Whatman)

3.Pipettes and disposable tips (Socorex; Finnipipette (Labsystems); Pasteur pipettes (Copan Italia)

4.Measuring cylinders

5.Staining dish and rack

6.Staning tray

7. Pressure Cooker (Tower)

8.Bunsen Burner

9.PAP pen (DAKO)

10.Rocker (A600 Rocker-Denley)

11.Stirrer (Janke and Kunkerl IKA-Labortechnik)

12.Timer

13.Fume Cupboard (WS-6 Downflow Workstation Labcaire)

14.Cover slips (22x22mm)

3.2.5.3 Solutions

A. Reagents, Chemicals, Serum and Antibodies

1.Tris analar (BDH)

3.Histoclear (BS &S Scotland Ltd)

4.Industrial Methylated Spirit (IMS99)

5.Methanol (Rathburn Chemicals Ltd)

6.6% Hydrogen peroxide (Hilcross Pharmaceuticals)

7.Hydrochloric Acid Analar (Merk)

8.Haemotoxylin (Sigma HHS-80)

9.Xylene (BDH)

10.DePeX (Merk)

11. Lithium Carbonate (BDH)

12. Rabbit serum (SAPU)

13.Monoclonal p53 protein 1801 (Novacastra)

14.Biotinylated Rabbit anti-Mouse immunoglobulins (Dako)

15.StreptABComlex/peroxidase kit (Dako)

16.Presept(Johnson & Johnson)

B. Stock Solutions

1.0.5M Tris buffer pH 7.6

Dissolve 60.72gms of Tris analar in 500mls of Distilled Water. Adjust pH to 7.6 with 1N Hydrochloric Acid and make up volume to 1 Litre.

2.0.1M Citrate buffer

Dissolve 2.1gms of citric acid monohydrate in 900mls of distilled water and adjust pH to 6.0 with 2MNa OH (approximately 13 ml). Make up to 1000ml with water.

3.70% IMS 99

Add 700mls of IMS99 to 300mls of water

C.Working Solutions

1. 0.005M Tris buffered saline pH 7.6 (TBS)

Dilute 0.5M Tris buffer 1/100 with 0.9% sodium chloride

2.0.01 Citrate buffer

Dilute 0.1M Citrate buffer 1/10 with water

3. 0.5% Hydrogen peroxide in methanol

Add 25mls of 6% hydrogen peroxide to 275mls of methanol

4.1% acid alcohol

Add 10 mls of concentrated Hydrochloric acid to 990mls of 70% IMS99.

3.Normal Rabbit serum (NRS/TBS)

Filter normal rabbit serum and dilute 1:10 with TBS 0.005M

4. Antibody dilutions

a.p53 1/40 in NRS/TBS (primary antibody)

b.Biotinylated Rabbit anti Mouse 1/500 in NRS/TBS (secondary antibody)(RAM)

c.Sreptavidin-biotin-peroxidase complex (ABC)

A Streptavidin	1µl
B Biotinylated horseradish peroxidase	1µl
TBS	100µl

5.Substrate

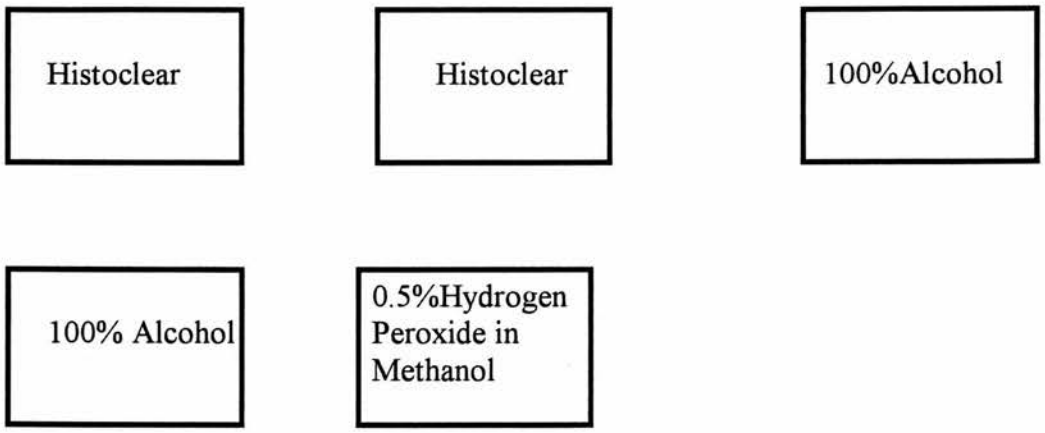
DAB

1.0.05M Tris ph7.6	10mls
2.Diaminobenzidine	10mg
3.Imidazole	1 flake
4.6% Hydrogen peroxidase	60µl

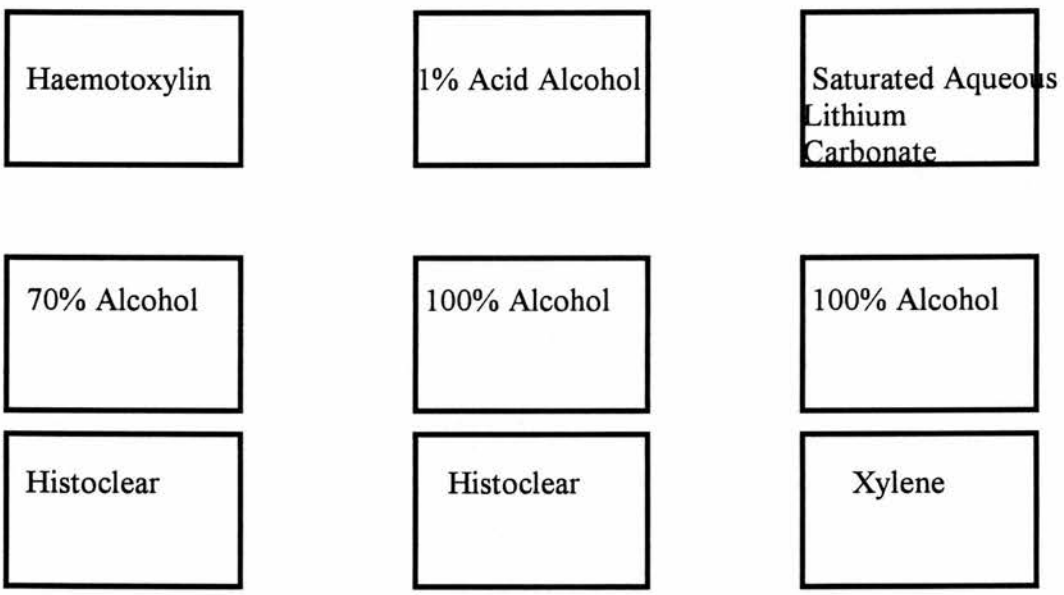
Prepare fresh

6. Prepare two sets of square glass dishes with contents as below

a) Glass dishes for dewaxing slides



b) Glass dishes for haemotoxylin staining



3.2.5.4 Methods

A. Dewaxing

Formalin fixed biopsies were processed by standard histological techniques, embedded in wax and sectioned. Three sections from each biopsy were taken for p53 immunostaining. One section was reserved and one section from the remaining pair was labelled NPA (No Primary Antigen). This provided a homologous negative control in each experiment; a positive control was taken from breast tissue. The

slides were placed in the staining racks and placed in the glass dish containing Histoclear overnight to ensure adequate dewaxing. The next morning they were placed sequentially into the two glass dishes containing 100% alcohol for 10 minutes each. Finally they were moved into the dish containing 0.5% hydrogen peroxide in methanol for a further 10 minutes and subsequently washed in running tap water.

B. High temperature antigen retrieval

One and a half litres of 0.01M Citrate buffer were placed into the pressure cooker. The lid was placed over loosely and the solution gently heated over a Bunsen burner until gently boiling. The rack with the sections was placed into the buffer and the lid closed tightly. Heating was continued until there was a continuous flow of steam from the pressure valve and continued for a further minute. After one minute, the pressure cooker was removed from the heat and placed under a running tap. The steam was gradually released and the lid then removed. The sections were placed into cold water and rinsed for five minutes and then rinsed for a further five minutes in TBS.

C. Antibody staining

The slides were removed from the rack and a circle drawn around each section with a PAP pen to form a reservoir for the antibody solution. Each slide was placed on the staining tray and each section was covered completely with NRS for 10 minutes. Sections labelled NPA were left covered with NRS for a further 30 minutes. All other sections had excess serum removed and replaced with the primary antibody (p53) for 30 minutes. At this stage all slides were replaced in the staining rack and rinsed in TBS for ten minutes, replacing the solution after five minutes. Excess TBS

was removed from the slides, which were again placed on the staining tray and covered with the secondary antibody (RAM) for another 30 minutes. The slides were washed in TBS for a further ten minutes, as before, then excess TBS removed and replaced with the tertiary antibody (ABC) for a further 30 minutes.

D. Development of peroxidase activity with DAB

After another two five minute rinses in TBS, the slides were placed on the staining racks which had been placed in the fume cupboard. Each section was covered with DAB for exactly 10 minutes. Excess DAB was removed from each slide and collected in a waste bottle, which was subsequently treated with Presept tablets. The slides were placed in the staining rack and washed in running tap water for 10 minutes.

E. Staining with Haemotoxylin

The sections in the staining rack were passed sequentially through the glass dishes arranged for haemotoxylin staining. Then they were placed into haemotoxylin for 1 minute, washed in running tap water for 15 seconds, dipped twice into 1%acid alcohol, washed in running tap water for 15 seconds and placed into saturated aqueous lithium carbonate until blue. Following this they were again washed in running tap water for 1 minute, placed into 70% alcohol for 5 minutes, placed into the two dishes of 100% alcohol for 5 minutes each, and then into the two dishes of Histoclear each for 5 minutes. Finally the sections were placed into Xylene.

F. Coverslipping sections

The coverslips were carefully cleaned and then placed on a clean piece of tissue. A streak of DPX was placed over the coverslip using the glass rod, of adequate size to

cover the stained section. The section was removed from Xylene and with a tissue the back of the slide carefully dried with a tissue. The section was carefully lowered onto the coverslip and gentle pressure was applied to spread the DPX. Any air bubbles were removed by applying gentle pressure to the coverslip. The coverslipped sections were left to dry overnight.

3.2.6 Flow cytometry

3.2.6.1 Principal of method

Propidium Iodide was used to bind to the DNA. It intercalates into double-stranded nucleic acids, and is excited by the 488nm line of an argon-ion laser and fluoresces red. Because viable cells exclude it, cells were permeabilized before adding the dye. It also binds to double-stranded RNA, which was deactivated first by treatment with RNase. As the instrument alignment is critical for DNA measurement it was checked frequently using a standard sample of fresh peripheral blood sample stained in the same way.

3.2.6.2 Apparatus

1. Glass tubes

2.Pipettes

3.Fine Wire Mesh sieve

4.Centrifuge

5.Fax Flow cytometer

3.2.6.3 Solutions

1.Propidium Iodide (PI)

25mg PI in 10mls Isoton

2-5μl in 300μl for viability

2.TRITON

1ml of concentrated PI-2.5mg/ml into 5% TRITON X 100.

Triton 0.5ml to 10 mls.

3.RNASE

4. Eales solution

3.2.6.4 Methods

A. Preparation of Samples

Samples were thawed and processed immediately. They were ground over a wire mesh sieve to disaggregate the tissue and suspended in Eales solution. The samples were spun in the centrifuge at 2000rpm for 5 minutes. The supernatant was taken off and they were resuspended to 500μl in Eales solution. 125μl of PI Triton (1/10) and 1mg (i.e. 100μl) Rnase was added to the samples.

B. Running of Samples

Samples were analysed using a FAX machine until 10,000 cells had been counted.

3.3 Statistical analysis

Mann Whitney and Chi-squared tests were used as appropriate.

3.4 Results

3.4.1 Complications

Two patients experienced mild retrosternal chest pain following the initial APC treatment. This was self-limiting and required no specific treatment.

3.4.2 Endoscopist's Description

The endoscopist described the extent of the Barrett's oesophagus during each endoscopy. Although, the oesophagus had been tattooed at 12 o'clock, the ink mark could not be visualised at the two month follow up. (Figures 3.3 and 3.4 and Table 3.1).

Figure 3.3 Patient One. Endoscopic pictures at baseline (above) and 6/12 (below) showing obliteration of tongue of Barrett's at 5 o'clock.

Figure 3.4 Patient Six. Endoscopic pictures at baseline (above) and 6/12(below) showing formation of multiple squamous islands.

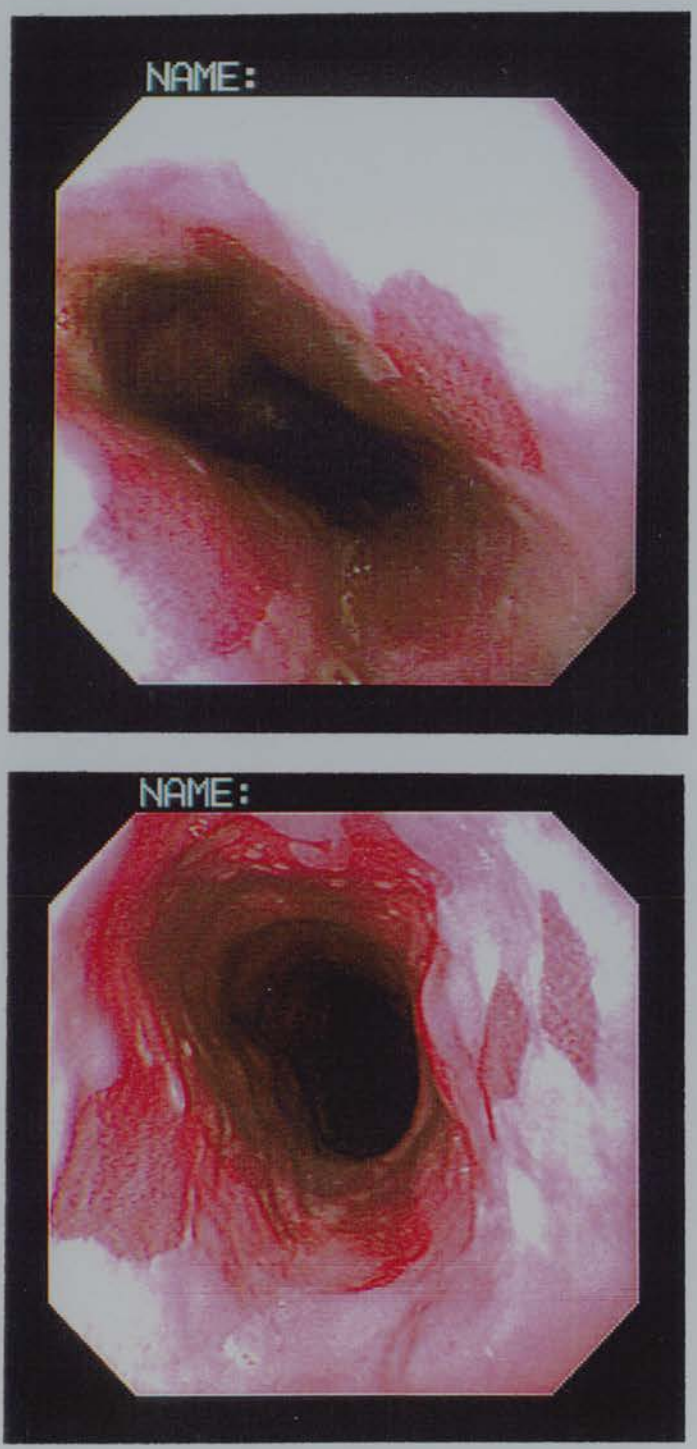


Table 3.1 Endoscopic appearance-Endoscopist's description

	TREATED SIDE			UNTREATED SIDE		
NUMBER	BASELINE	2/12	6/12	BASELINE	2/12	6/12
ONE	3cm CLO (2 tongues)	One remaining tongue of CLO	As 2/12	3cm CLO	3cm CLO	3cm CLO
TWO	2cm CLO	No CLO remaining except one small island	As at 2/12	2cm CLO	No change	No change
THREE	10 cm CLO	Several islands of squamous tissue intruding into CLO for 3cms	Persisting squamous islands.	10cm CLO	No change	No change
FOUR	12cm CLO	Multiple islands of Squamous tissue within CLO	Persisting squamous islands	12cm CLO	No change	No change
FIVE	5cm CLO	Extension of squamous tongue into area of CLO	Persisting squamous tongue into area of CLO	5cm CLO	No change	No change
SIX	10cm CLO	Multiple islands of squamous tissue	Persisting squamous islands	10cm CLO	No change	No change
SEVEN	5cm CLO	Improved	Same as baseline	5cm CLO	No change	No change
EIGHT	2cm CLO	Slight improvement	As at 2/12	2cm CLO	No change	No change
NINE	5cm CLO	Improved	2 short tongues of CLO	5cm CLO	No change	2 tongues CLO
TEN	5cm CLO & islands	Obvious squamous island and scarring		5cm CLO with islands	No change	
ELEVEN	5cm CLO (tongues)	Improvement in tongues of CLO		5cm CLO	No change	
TWELVE	5cm CLO & 2 islands	Some improvement		5cm CLO	No change	

3.4.3 Histopathology

The number of biopsies from each patient exhibiting intestinal metaplasia or squamous epithelium were counted. Other histological diagnoses such as fundal, cardiac or junctional epithelium were not considered. Biopsies containing both intestinal metaplasia and squamous epithelium were classified as squamous epithelium. Where biopsies revealed squamous epithelium overlying intestinal metaplasia these were classified as "squamous epithelium". Findings in treated and untreated sides of the oesophagus are shown in Tables 3.2 & 3.4. Two further analyses are also shown. All the biopsies from the treated and untreated sides are then considered together and finally only the most proximal biopsies are analysed (Tables 3.3 & 3.5). There was a statistically significant difference in the proportion of proximal biopsies showing intestinal metaplasia at six months as compared to baseline. There was a also a significant increase in the number of biopsies from the treated side showing squamous epithelium at both two and six months as compared to baseline. This comparison was not significantly different for untreated side.

Two patients (patients 10 and 11) had low grade dysplasia within pre-treatment biopsies. This was not observed in biopsies taken at two months. Histopathology identified three patients with squamous epithelium overlying intestinal metaplasia, following treatment with APC (Figure 3.5). In one patient this became apparent after six months; in the second patient it was seen at two months but was not present at six months; and in the third patient buried glands were seen at two months, further follow-up not being available.

Table 3.2 Pathology-Proportion of biopsies from each patient showing intestinal metaplasia
Chi-squared tests comparing results at two and six months with those at baseline are shown.

	TREATED SIDE			UNTREATED SIDE		
PATIENT NO.	BASELINE	2/12	6/12	BASELINE	2/12	6/12
ONE	1/4 (25%)	1/4 (25%)	2/4 (50%)	2/4 (25%)	0/4 (0%)	0/4 (0%)
TWO	0/4 (0%)	0/3 (0%)	0/2 (0%)	0/4 (0%)	0/4 (0%)	0/2(0%)
THREE	2/6 (33%)	2/6 (33%)	3/6 (33%)	3/6 (33%)	4/6(33%)	6/6 (100%)
FOUR	3/5 (60%)	1/6 (17%)	2/6 (33%)	1/6 (17%)	6/6 (100%)	0/6 (0%)
FIVE	2/4 (50%)	3/4 (75%)	1/4 (25%)	3/4 (75%)	2/4(25%)	2/4 (25%)
SIX	5/6 (83%)	2/6 (33%)	2/6 (33%)	6/6 (100%)	4/6 (66%)	5/6(83%)
SEVEN	1/4(25%)	3/4 (75%)	1/4 (25%)	0/4 (0%)	1/3 (33%)	1/4(25%)
EIGHT	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	1/2(25%)
NINE	0/4 (0%)	1/4 (25%)	0/4 (0%)	1/4 (25%)	1/4 (25%)	1/4(25%)
TEN	3/4 (75%)	1/3 (33%)		4/4 (100%)	0/4 (0%)	
ELEVEN	2/4 (50%)	0/4 (0%)		1/4 (25%)	0/4(0%)	
TWELVE	0/4 (0%)	1/4 (25%)		0/4 (0%)	3/3(100%)	
TOTAL	19/51(37%)	15/50(30%)	11/38(29%)	21/52(40%)	21/50(42%)	16/38(42%)
P Value (Chi-squared)		0.441	0.412		0.412	0.870

Table 3.3 Pathology-Proportion of biopsies from each patient showing intestinal metaplasia (Pooled Results)
Chi-squared tests comparing results at two and six months with those at baseline are shown.

	ALL BIOPSIES			PROXIMAL BIOPSIES		
PATIENT NO.	BASELINE	2/12	6/12	BASELINE	2/12	6/12
ONE	3/8	1/8 (12%)	2/8 (25%)	2/4	¼	0/4
TWO	0/8	0/7 (0%)	0/4 (0%)	0/4	0/4	0/4
THREE	5/12	6/12 (50%)	9/12 (75%)	¼	0/4	2/4
FOUR	4/11	7/12 (58%)	2/12 (17%)	2/4	2/4	0/4
FIVE	5/8	5/8 (62%)	3/8 (38%)	4/4	¼	0/4
SIX	11/12	6/12 (50%)	7/12 (58%)	¾	0/4	¼
SEVEN	1/8	4/7 (57%)	2/8 (25%)	0/4	¾	0/4
EIGHT	0/4	0/4 (0%)	¼ (12%)	0/4	0/4	¼
NINE	1/8	2/8 (25%)	1/8 (12%)	0/4	¼	¼
TEN	7/8	1/7 (14%)		¾	0/3	
ELEVEN	3/8	0/8 (0%)		1/4	0/4	
TWELVE	0/8	4/7 (57%)		0/4	1/3	
TOTAL	40/101(39%)	36/100(36%)	27/76(36%)	16/48(33%)	9/46(19%)	5/36(14%)
P Value (Chi-squared)		0.598	0.580		0.131	**0.042**

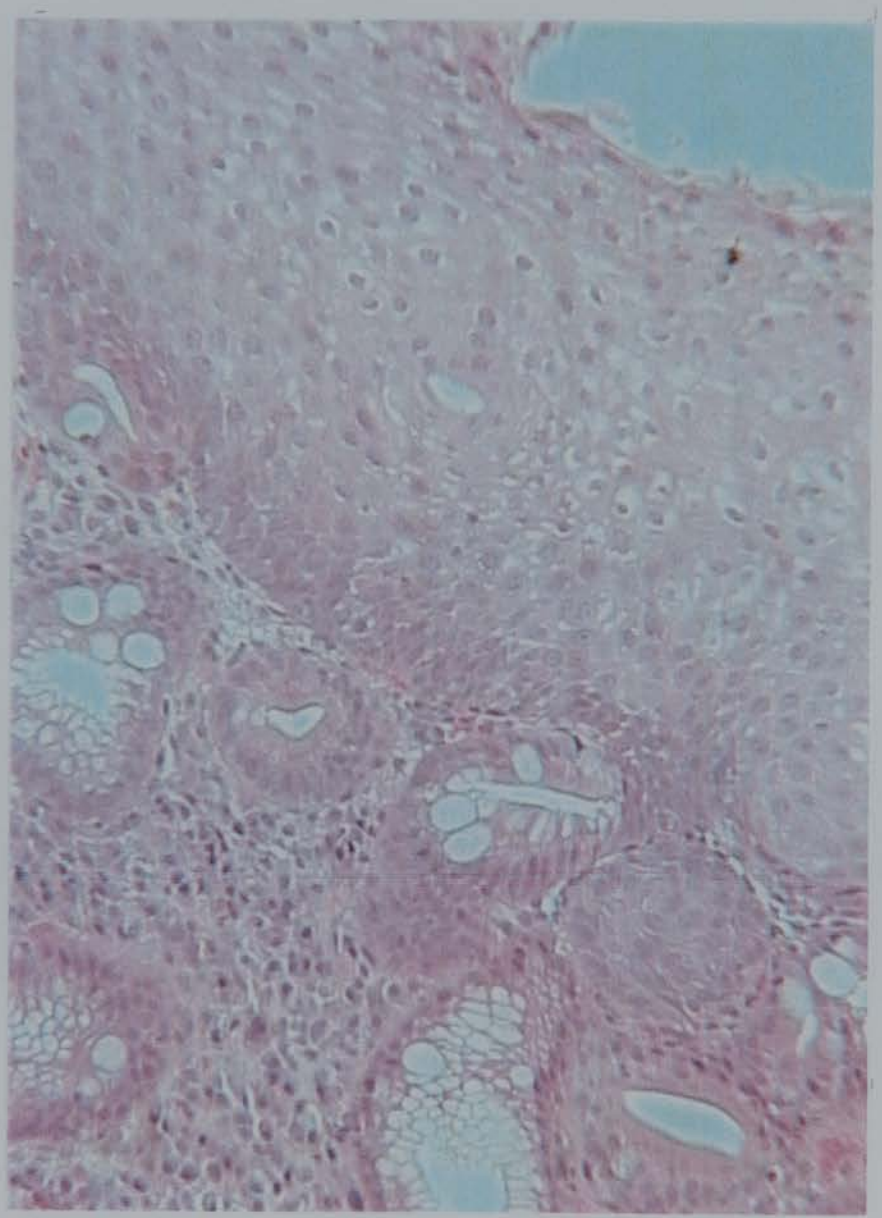
Table 3.4 Pathology-Proportion of biopsies from each patient showing squamous epithelium
Chi-squared tests comparing results at two and six months with those at baseline are shown.

	TREATED SIDE			UNTREATED SIDE		
PATIENT NO.	BASELINE	2/12	6/12	BASELINE	2/12	6/12
ONE	¾(75%)	1/4(25%)	2/4(50%)	2/4(50%)	3/4(75%)	0/4(0%)
TWO	0/4(0%)	2/3(67%)	1/2(50%)	0/4(0%)	0/4(0%)	1/2(50%)
THREE	0/6(0%)	3/6(50%)	3/6(50%)	0/6(50%)	2/6(33%)	0/6(0%)
FOUR	0/5(0%)	4/6(67%)	4/6(67%)	3/6(50%)	0/6(0%)	6/6(100%)
FIVE	0/4(0%)	1/4(50%)	1/4(25%)	0/4(0%)	2/4(50%)	0/4(0%)
SIX	1/6(17%)	4/6(67%)	3/6(67%)	0/6(0%)	2/6(33%)	1/6(17%)
SEVEN	0/4(0%)	0/4(0%)	1/4(25%)	0/4(0%)	0/4(0%)	2/4(50%)
EIGHT	0/2(0%)	0/2(0%)	1/2(25%)	0/2(0%)	2/2(100%)	0/2(0%)
NINE	4/4(100%)	1/4(25%)	2/4(0%)	3/4(75%)	¼(25%)	0/4(25%)
TEN	¼(25%)	2/3(100%)		0/4(0%)	3/4(75%)	
ELEVEN	¼(25%)	2/4(50%)		2/4(50%)	1/4(25%)	
TWELVE	0/4(0%)	2/4(50%)		0/4(0%)	0/3(0%)	
TOTAL	10/51(20%)	22/50(44%)	18/38(47%)	10/52(19%)	16/51(31%)	10/38(26%)
P Value (Chi-squared)		**0.009**	**0.005**		0.156	0.425

Table 3.5 Pathology-Proportion of biopsies from each patient showing squamous epithelium (Pooled results)
Chi-squared tests comparing results at two and six months with those at baseline are shown.

	ALL BIOPSIES			PROXIMAL BIOPSIES		
PATIENT NO.	BASELINE	2/12	6/12	BASELINE	2/12	6/12
ONE	5/8	4/8	2/8	2/4	¾	2/4
TWO	0/8	2/7	2/4	0/4	2/4	2/4
THREE	0/12	5/12	3/12	0/4	4/4	2/4
FOUR	3/12	4/12	10/12	2/4	2/4	4/4
FIVE	0/8	3/8	1/8	0/4	3/4	¼
SIX	1/12	6/12	4/12	1/4	4/4	¾
SEVEN	0/8	0/8	3/8	0/4	0/4	2/4
EIGHT	0/4	2/4	¼	0/4	2/4	¼
NINE	7/8	2/8	2/8	4/4	0/4	2/4
TEN	1/8	5/7		1/4	¾	
ELEVEN	3/8	3/8		3/4	¾	
TWELVE	0/8	2/7		0/4	2/3	
Total	20/103(19%)	38/101(38%)	28/76(37%)	13/48(27%)	28/47(60%)	19/36(53%)
P Value(Chi-squared)		**0.004**	**0.009**		**0.001**	**0.017**

Figure 3.5 Intestinal metaplasia buried underneath squamous epithelium following APC treatment (x25)



3.4.4 p53 Staining

All the biopsies were examined by two blinded observers (H.J Dallal and A. Smakov). They were in agreement over the broad distinction between negative and positive biopsies, on the basis of nuclear staining. All the positive controls were strongly positive and the negative controls were all negative (Figures 3.6-3.9).

Subsequently the staining was graded by a single observer (A. Smakov), into strongly positive, positive or weakly positive. The number of p53 positive biopsies, regardless of staining grade and histology, for the untreated and treated sides of the oesophagus was analysed (Table 3.6). The total number of strongly staining biopsies was also considered (Table 3.7)

Figure 3.6 Nuclear p53 staining in specialised intestinal metaplasia (x25)

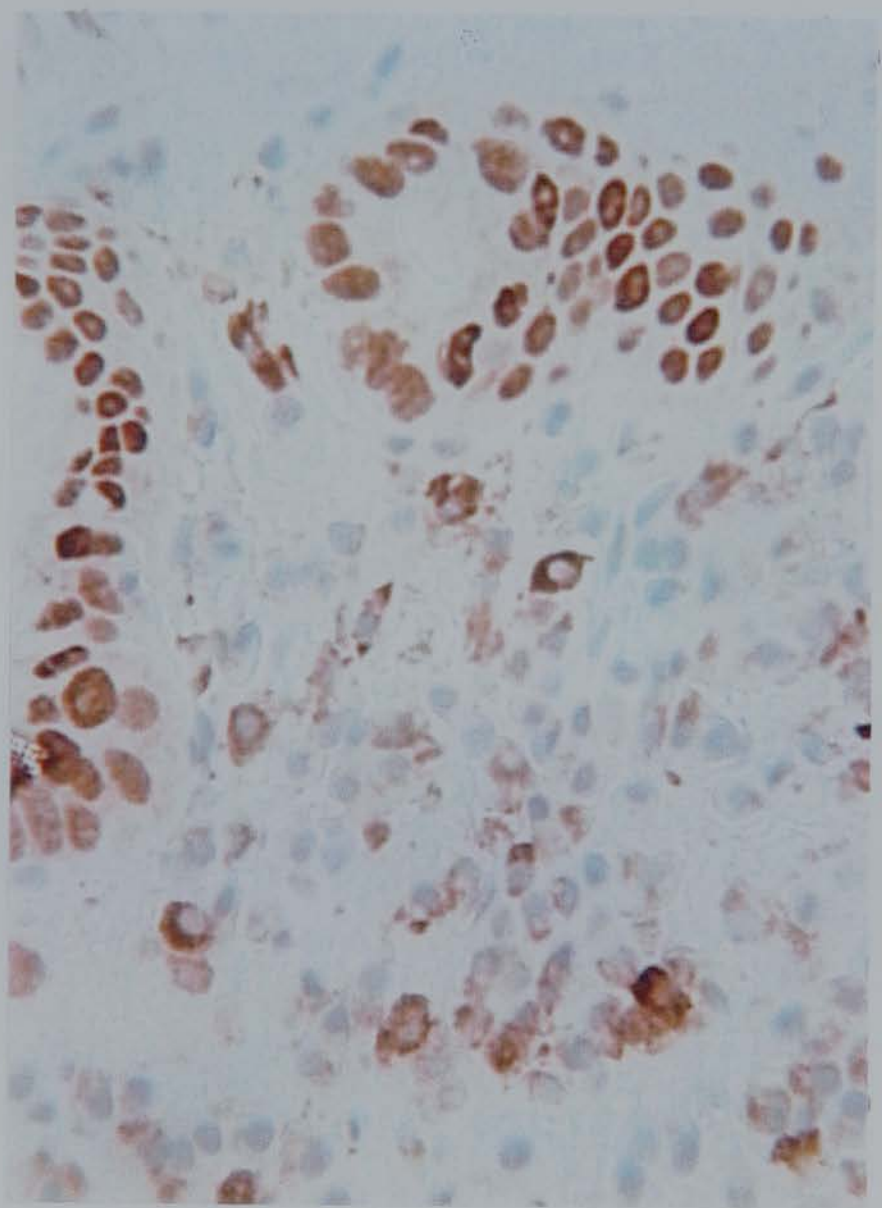


Figure 3.7 Nuclear p53 staining of junctional epithelium (x10)

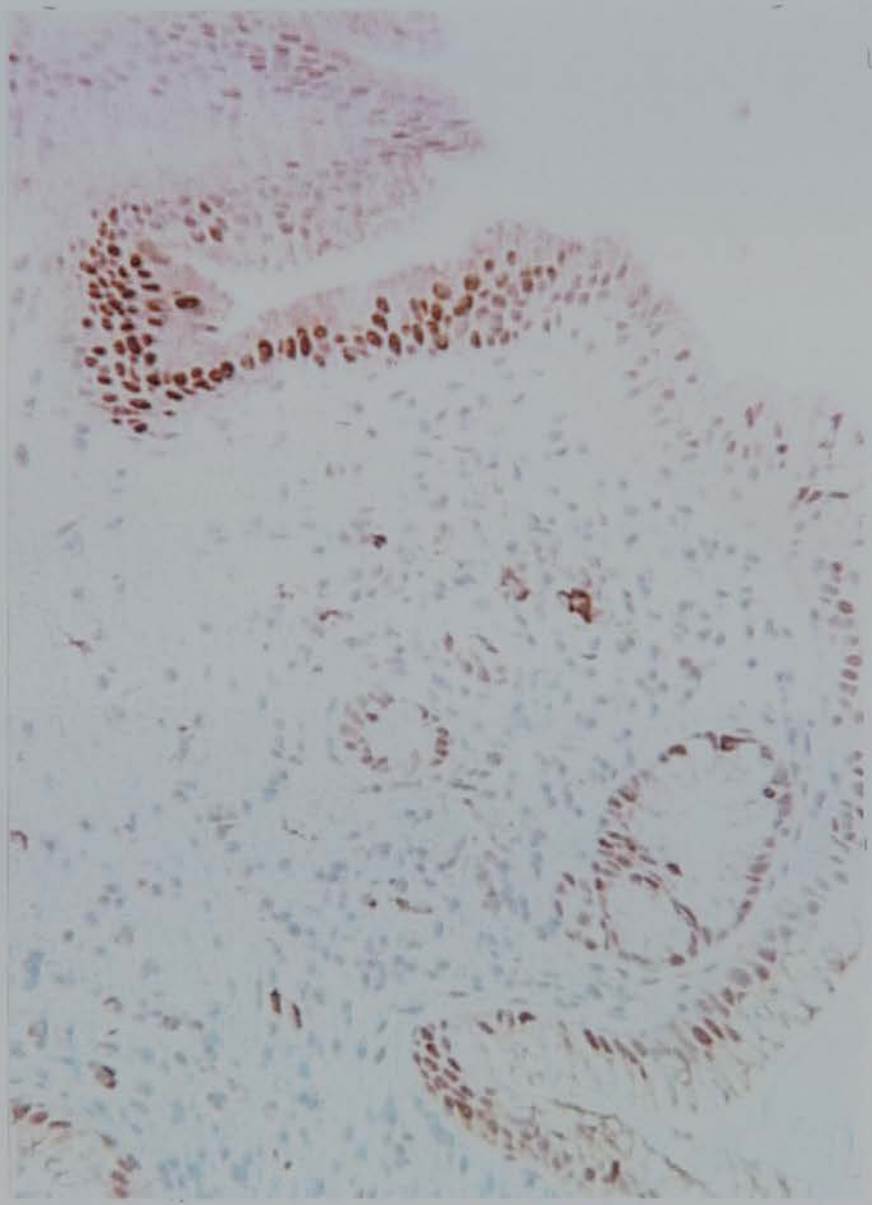


Figure 3.8 Perinuclear p53 staining in specialised intestinal metaplasia (x25)

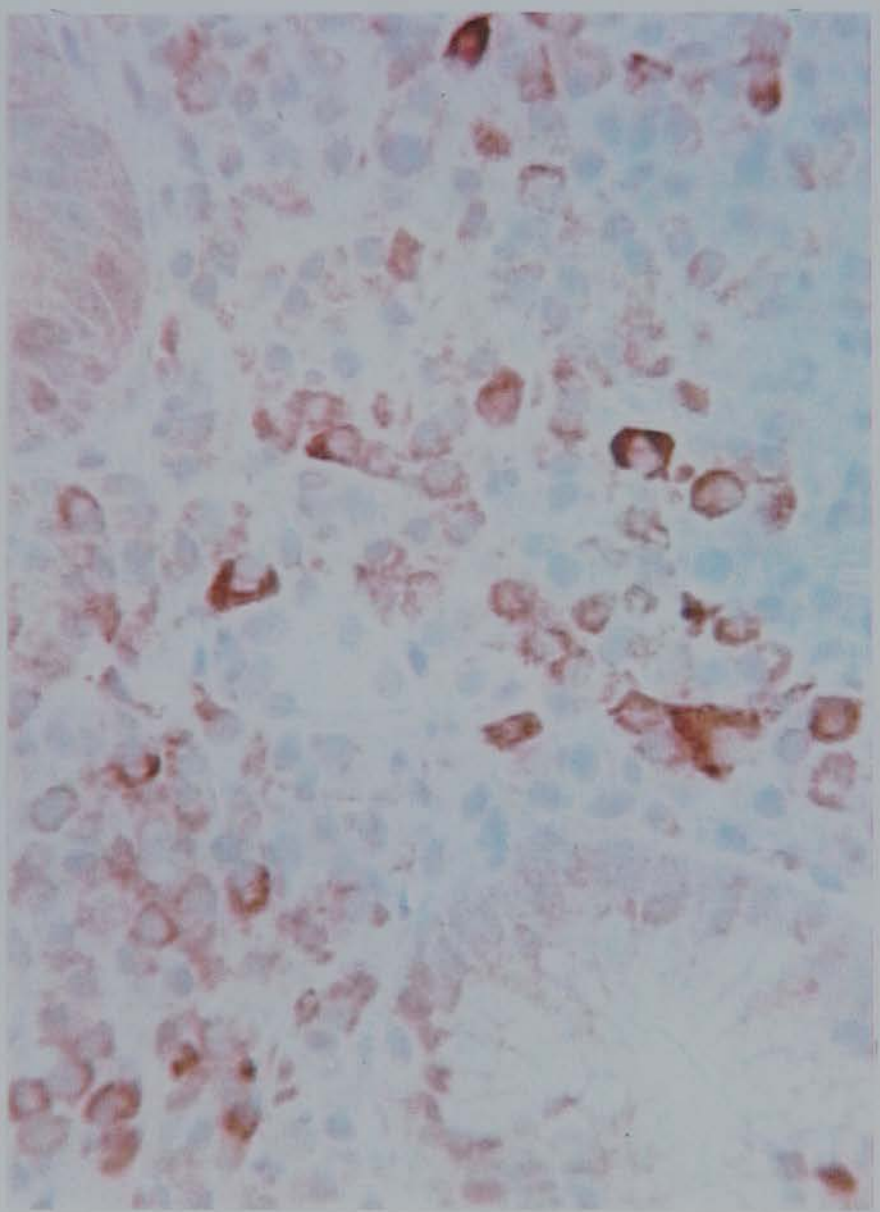


Figure 3.9 Apical p53 staining of gland buried underneath squamous epithelium

Table 3.6 p53 Staining-Number of positive biopsies per patient
Chi-squared tests comparing results at two and six months with those at baseline are shown.

	TREATED SIDE			UNTREATED SIDE		
PATIENT NO.	BASELINE	2/12	6/12	BASELINE	2/12	6/12
ONE	¼	0/4	1/4	1/4	1/4	0/4
TWO	¼	0/4	0/4	0/4	0/4	0/4
THREE	4/6	1/6	1/6	3/6	0/6	0/6
FOUR	0/6	1/6	3/6	0/6	0/6	4/6
FIVE	¼	1/4	1/4	1/6	1/6	¼
SIX	0/6	0/6	1/6	0/6	0/6	1/6
SEVEN	0/4	0/4	0/4	0/4	1/4	¼
EIGHT	0/2	0/2	0/2	0/2	0/2	0/2
NINE	0/4	0/4	2/4	0/4	0/4	0/4
TEN	¼	0/4		0/4	0/4	
ELEVEN	¼	1/4		0/4	1/4	
TWELVE	0/4	0/4		0/4		
TOTAL	9/54 (17%)	4/54(7%)	9/40(22%)	5/54(9%)	4/54(7%)	7/40(18%)
P value (Chi-squared)		0.14	0.40		0.07	0.24

Table 3.7 p53 Number of strongly positive staining biopsies per patient.

	ALL BIOPSIES		
PATIENT NO.	BASELINE	2/12	6/12
ONE	1	0	0
TWO	0	0	0
THREE	3	0	0
FOUR	0	1	0
FIVE	0	0	0
SIX	0	0	0
SEVEN	0	0	0
EIGHT	0	0	0
NINE	0	0	0
TEN	0	0	
ELEVEN	0	0	
TWELVE	0	0	
TOTAL	4	1	0

3.4.5 Flow cytometry

All cell populations analysed were diploid (Figure 3.10) Repeats were performed on the duplicate biopsies when flow cytometry had revealed too few cells present or excessive interference. In these cases the repeated results are reported here. The percentage of cells from each biopsy in the S and G0/1 phases are shown (Table 3.8 and 3.9).

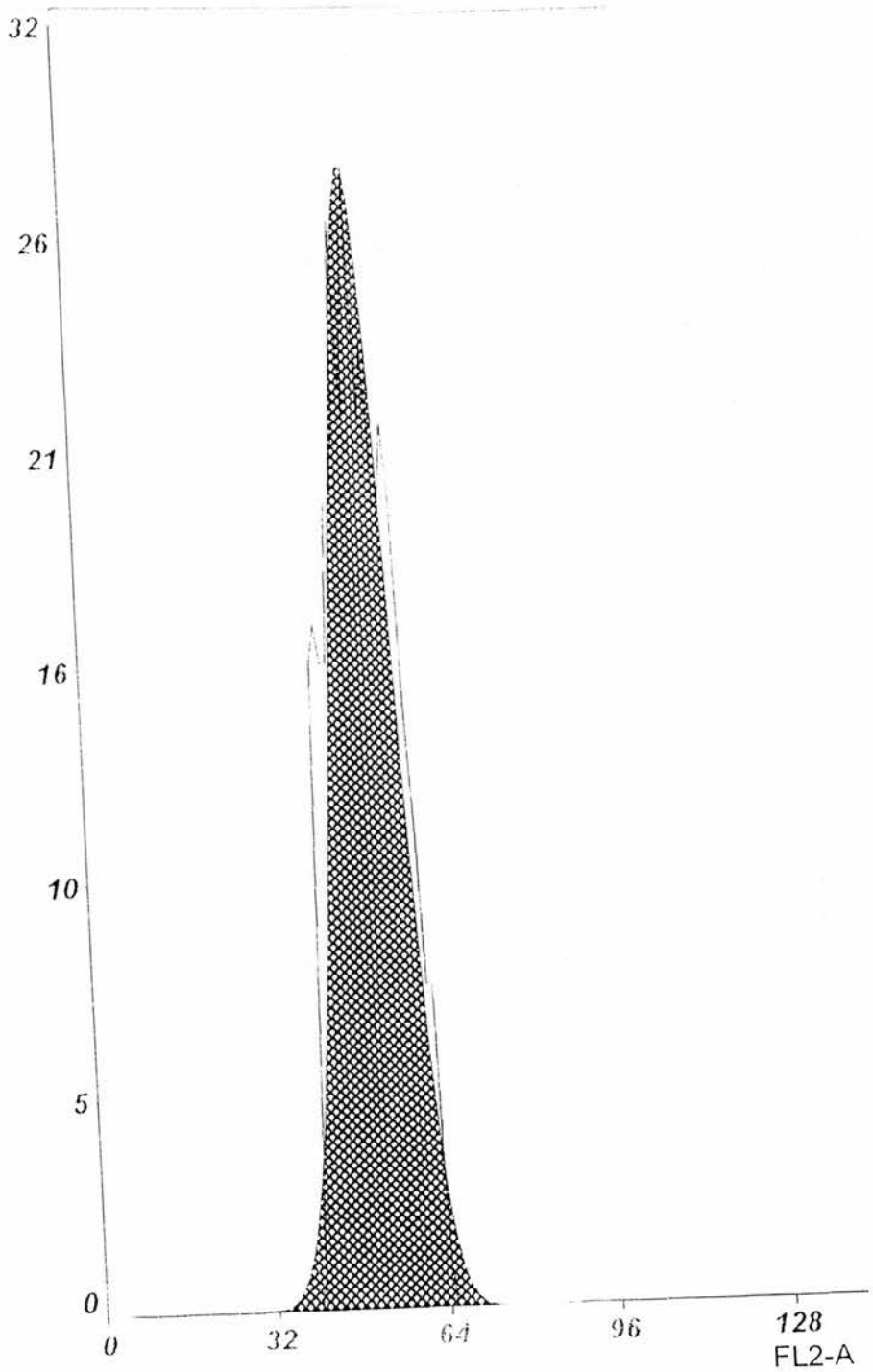
Table 3.8 Flow cytometry-S phase (%).
Mann Whitney tests comparing results at two months and six months with baseline results are shown

	TREATED SIDE			UNTREATED SIDE		
PATIENT NO.	BASELINE	2/12	6/12	BASELINE	2/12	6/12
ONE	5.9	3.6	5.8	13.5	5.6	2.1
TWO	2.9	21.5	7.5	4.1	----	3.9
THREE	7.7	5.6	3.6	7.1	4.8	8.9
FOUR	4.7	4.9	0.7	5.0	5.0	4.1
FIVE	5.5	11.1	3.1	2.2	0.0	1.8
SIX	10.8	3.5	2.9	7.6	0.0	12.1
SEVEN	2.6	4.7	6.2	2	3	6.6
EIGHT	1.3	2.5	1	11.7	3	16.8
NINE	10.7	10.4	1.9	23.9	7.2	15.8
TEN	3.2	1.2		1.8	7.6	
ELEVEN	0	10.1		11.9	23.4	
TWELVE	11.6	10.7		5.2	0	
Mean (SD)	5.57(3.89)	7.48(5.63)	3.63(2.39)	8.0(6.42)	5.42(6.57)	8.01(5.74)
Median (Range)	5.10(0-11.6)	5.25(1.2-21.5)	3.1(0.7-7.5)	6.15(1.8-23.9)	4.80(0-23.4)	6.6(1.8-16.8)
P Value (Mann Whitney)		0.583	0.319		0.229	0.972

Table 3.9 Flow cytometry G0/1 phase (%)
Mann Whitney tests comparing results at two months and six months with baseline results are shown

	TREATED SIDE			UNTREATED SIDE		
PATIENT NO.	BASELINE	2/12	6/12	BASELINE	2/12	6/12
ONE	90.5	94.8	94.2	80.6	94.4	97.1
TWO	89.4	73.3	92.5	88.9	-	94.7
THREE	80.6	94.4	96	77.2	95.2	85.9
FOUR	89.4	95.1	98.7	95	95	94
FIVE	86.5	88.9	94.9	95.1	96.5	98.2
SIX	81.3	95.5	96.4	88.9	94.7	85.1
SEVEN	96.8	92.4	91.4	96.7	95.7	93.6
EIGHT	98.7	96.9	98.6	85.7	96.8	76.5
NINE	87.6	87.4	60.4	75.9	92.8	81.4
TEN	96.8	86.9		98.2	89.2	
ELEVEN	95.8	89.9		85.7	73.2	
TWELVE	87.8	71.1		93.3	100	
Mean (SD)	90.1(5.9)	88.9(8.5)	91.5(11.9)	88.4(7.6)	93.1(7.1)	89.6(7.6)
Median (Range)	89.4(80.6-98.7)	91.1(71.1-96.9)	94.9(60.4-98.7)	88.9(75.9-98.2)	95.0(73.2-100)	93.6(76.5-98.2)
P Value(Mann-Whitney)		0.885	0.200		0.124	0.776

Figure 3.10 Flow Cytometry-Diploid population



3.4.6 Patient Eleven

One patient (patient eleven) presented with dysphagia prior to his six month follow up. Endoscopy showed a stricture at the gastro-oesophageal junction and histology confirmed this to be an adenocarcinoma. Tables 3.10 & 3.11 detail this patient's histology, p53 staining and flow cytometry at baseline and two month follow-up. The treated side of the oesophagus is shown in bold.

Table 3.10 Patient eleven. Histology and p53 staining.

BIOPSY NO.	PATHOLOGY ONE	P53 ONE	PATHOLOGY TWO	P53 TWO
	4436		6743	
1 PR1	**Squamous**		**Squamous**	
2 PR2	**Int Metap+ Low Grade Dysplasia**		**Squamous**	**POSITIVE +**
3 PL3	Squamous		Squamous	POSITIVE +
4 PL4	Squamous		Gastric	
5 DR1	**Gastric+ Low Grade Dysplasia**	**POSITIVE +**	**Junctional/cardiac**	
6 DR2	**Gastric**		**Junctional/cardiac**	
7 DL3	Gastric		Gastric	
8 DL4	Gastric +Low Grade Dysplasia		Junctional/cardiac	

Table 3.11 Patient eleven. Flow cytometry.

	Code	G1channel	G0/1%	S%
22SEP002	**One R**	**50.9**	**92.5**	**7.5**
DALA28S001	**One R**	**49.9**	**95.8**	**0**
22SEP001	One L	45.5	93.8	5.4
DALA28S002	One L	47.3	85.7	11.9
22SEP009	Two L	54.7	73.2	23.4
22SEP010	**Two R**	**61.0**	**93**	**0**
DALA28S004	**Two R**	**47.8**	**89.9**	**10.1**

3.5 Discussion

Treatment of CLO with APC appears to be a safe treatment with only two of twelve patients experiencing self-limiting retrosternal chest pain following therapy.

The endoscopist's description subjectively reported an improvement in the appearance of the treated Barrett's oesophagus in all patients, and this was confirmed by comparison of the endoscopic photographs.

There was a trend for an increase in the number of squamous biopsies and a decrease in the number of biopsies showing intestinal metaplasia in the treated side as compared to the untreated side. If both sides are considered together, negating the internal control, there is no change in the number of biopsies showing intestinal metaplasia, but a trend for an increase in the number of squamous biopsies. Considering only the most proximal biopsies, there was again a trend for an increase in the number of squamous biopsies and a decrease in biopsies showing intestinal metaplasia.

One of the problems inherent in using an internal control is the orientation of the biopsies. The tattooing was not visible at two months and it was difficult to judge accurately which was the treated and which was the untreated sides. We endeavoured to overcome this problem by analysing all the biopsies together, thus negating the internal control but permitting an overall view of changes in the histology. Proximal biopsies were separated out to exclude the distal biopsies which may represent areas of the oesophagus which had been inadequately treated with APC.

Intestinal metaplasia is a patchy finding in an area of Barrett's oesophagus. It is also possible that as it is a dynamic process, it may also change with time. These

problems introduce a sampling error into the results and also imply that the internal control may not be entirely static.

One of the most clinically relevant finding in the study is the discrepancy between the endoscopist's assessment of squamous reepithelialisation and the histologic findings in biopsy samples from these areas. This probably reflects the inherent inaccuracy of targeting the biopsy samples and the relative insensitivity of endoscopy in identifying epithelial type. This discrepancy between endoscopic appearance and histology also makes it difficult to assess the effectiveness of APC.

The finding of buried glands raises practical points with regard to the biopsy of these patients and histological interpretation of such biopsy samples. Histological confirmation of squamous re-epithelialisation is essential, and biopsy samples taken for this purpose must include underlying lamina propria and must not merely consist of free superficial strips of squamous epithelium because any underlying residual glandular mucosa would go undetected in such specimens.

Logically, it would seem that if the number of Barrett's glands present can be significantly reduced then the risk of cancer should also be reduced. This may be an over simplistic approach. It is possible that unless complete eradication of Barrett's epithelium can be reliably achieved the potential for neoplastic transformation in the remaining glands could occur.

Partial regression of Barrett's oesophagus is probably an inadequate end point when considering the efficacy of treatment of this condition in terms of preventing neoplastic progression. Sampliner et al report a case which seems to confirm this view [318]. In this report a patient with high-grade dysplasia within Barrett's oesophagus showed extensive squamous reepithelialisation after treatment with a

fundoplication and a high dose PPI. A subsequent oesophagogastrectomy was performed. Histology from the resected specimen showed two foci of intramucosal carcinoma within overlying squamous epithelium.

In this study no patient showed complete or even extensive squamous re-epithelialisation after one treatment with APC. It may be possible to achieve this with multiple treatments with APC and this should be an area for future research. Laethem et al reported their experience of multiple APC sessions in 31 patients with Barrett's oesophagus [319]. Complete eradication of Barrett's mucosa was only confirmed histologically in 61% of patients. At one year 47% of these patients had relapsing islands of intestinal metaplasia. It should also be remembered that APC is a difficult and time consuming therapeutic procedure and there are considerable practical implications if this technique is to be used outwith clinical trials to treat patients with CLO on a routine basis.

The aim of CLO ablation is to reduce the risk of development of oesophageal cancer. Even if it is possible to achieve complete re-epethelialisation of CLO the effect of this on the cancer risk will remain unknown until such treated patients have been followed-up for many years. Long-term follow-up will also permit assessment of the stability of the reepithelialisation or if there is a tendency for the CLO to re-occur with time.

Of great concern is patient number eleven who developed an oesophageal adenocarcinoma between his two and six month follow- up. His histology initially showed three out of eight biopsies with intestinal metaplasia with low grade dysplasia. At two month follow up this was no longer apparent. One biopsy initially

and two biopsies subsequently were weakly staining for p53. This was assumed to be of dubious significance as the staining was only weak. Flow cytometry if anything showed an improvement in the stability of the cell cycle at follow up.

In this small number of patients, only two of whom had low grade dysplasia, there were only a few biopsies that were staining positively for p53. These biopsies represented two out of the twelve patients (16%) with at least one strongly positive biopsy at baseline. This reflects the current literature which reports positive p53 staining in 0-15% of patients with intestinal metaplasia or low grade dysplasia [109;111;113]. Even if all the positive biopsies are considered (regardless of grade) these are too few to reach any conclusion of the effect of APC on p53 staining. Certainly, there does not appear to be any adverse effect on p53 staining.

No aneuploid cell populations were seen. This contrasts of 2.9-17.2% of aneuploidy in intestinal metaplasia reported elsewhere [117;118]. This possibly reflects the small number of patients used in this study. No overall change was present in either the S or G0/1 phase. Certainly there was no adverse effect of APC on the cell cycle.

This study has emphasised many of the practical difficulties in studies of endoscopic therapies for Barrett's oesophagus. Although treatment with APC is safe, the results of this study are disappointing. No patient showed extensive squamous re-epithelialisation, three showed buried glands, and one developed a carcinoma after a single treatment of APC. Further studies which assess long term cancer risk in patients treated with multiple applications of APC are required before it could be recommended outside experimental trials.

CHAPTER 4- Palliative treatment of oesophageal cancer

4.1 Introduction

Most patients who present with malignant oesophageal obstruction have irresectable disease, but require palliative treatment of dysphagia. A range of approaches including intubation with plastic [234], or expandable metal stents [240], Nd: YAG laser [215], photodynamic therapy [213], brachytherapy [197], chemoradiation [208] and palliative surgery are available, but none is ideal. Furthermore, there is often little relationship between relief of dysphagia and improved quality of life [296], probably because most patients have advanced disease, which results in pain, cachexia and general inanition.

Previous trials have shown that intubation with expandable stents is superior to stenting with plastic prosthesis [241]. It has also been shown that Nd: YAG laser treatment is superior to intubation with plastic stents [268]. One study comparing expandable metallic stents with laser therapy show that stent placement provided significantly better palliation of dysphagia, but provided no details on quality of life [269].

In the current study dysphagia, quality of life and cost were compared in a prospective, randomised clinical trial of laser therapy and expandable metallic stents.

4.2 Methods

4.2.1 Design

This was a prospective randomised trial in which patients with irresectable oesophageal cancer were randomised using sealed envelopes to laser therapy or

insertion of an expandable metallic stent. Dysphagia, Quality of Life scores, cost, complications and survival were the important end points.

4.2.2 Patient Details

Fifty-two patients referred for palliative treatment of dysphagia due to oesophago-gastric cancer were recruited. All had been assessed by both a specialist gastroenterologist and dedicated upper gastrointestinal surgeon who agreed that resectional surgery was inappropriate because of locally advanced disease (5 laser and 6 stent), lymph node involvement (4 laser and 3 stent), distant metastases (10 laser and 10 stent), or severe co-morbidity (6 laser and 8 stent).

All patients underwent upper gastrointestinal endoscopy with biopsy of the tumour, barium swallow to define the site and length of the stricture and computerised tomography of abdomen and thorax to define tumour size, local invasion and the presence of metastases.

4.2.3 Dysphagia

Dysphagia was scored on a scale of 0 to 4: 0=normal food intake, 1=difficulty with swallowing some solids, 2=able to swallow only soft food, 3= able to swallow liquids only, 4=complete dysphagia.

4.2.4 Quality of Life

Quality of life prior to intervention was assessed with three questionnaires. Patients were asked to complete The Hospital Anxiety and Depression Scale (HAD) (Appendix 1), the Short Form 36(SF36)(Appendix 2) and the EORTC QLQ -C30-OES 24 (Appendix 3).

HAD

The HAD questionnaire consists of questions each with a choice of graded responses. It has been found to be a reliable instrument for detecting states of depression or anxiety in a hospital population [317]. The subscales provide a valid measure of the severity of the emotional disorder.

SF 36

The SF36 is a general outcome measure. It uses eight health scales to measure three aspects of health - functional status, well being, and "overall evaluation of health". The responses to the questions on each scale are summed to provide eight scores between 0 and 100. It has been shown to be a valid measure of the health status of a wide range of patients [290].

EORTC QLQ -C30-OES 24

The EORTC QLQ -C30 core questionnaire consists of five functional scales, a global health scale and three symptom scales. In addition there are six single items assessing symptoms commonly found in cancer patients as well as a question about the financial impact of the disease. All scores are linearly transformed such that scales range from 0-100. A high score in the functional scales implies better function, whereas a high score in the symptom scale and single items means more symptoms. This basic questionnaire has previously been shown to have the sensitivity to distinguish between two clinically different groups of patients with oesophageal cancer [278].

The additional OES-24 consists of a further 24 questions specifically developed for patients with oesophageal cancer [320] It aims to improve the sensitivity and specificity of the core questionnaire to very small changes as a result of therapeutic

intervention. As it was developed recently it was introduced midway through this study.

4.2.5 Intervention

4.2.5.1 Endoscopic Laser therapy

Laser palliation was undertaken using either the ND: YAG fibrelase set at 90-100W for 1 second bursts (Fibrelase, Living technology, Glasgow, Scotland); the Argon Diode Laser set at 50W for 1 second bursts (Diomed 60W Surgical Diode Laser, Diomed Ltd, Cambridge); or Argon Plasma Coagulation set at 50W (APC 300 ERBE, Eleckromedizin GmbH, Tubingen) by one of two experienced endoscopists (Dr KR Palmer or Dr S Ghosh). Patients were sedated with a combination of intravenous pethidine (25-75mg) and midazolam (2-7.5mg, Roche Ltd). An Olympus GIFK endoscope (Keymed Ltd, Southend on Sea, UK) was used since this facilitates optimum directed therapy. Whenever possible oesophageal dilatation was avoided; when necessary the Olympus advanced dilators (Keymed Ltd) were used to dilate strictures.

Laser therapy was repeated at four to six week intervals, according to the degree of dysphagia.

4.2.5.2 Expandable metallic stent insertion

Expandable stents were inserted by an experienced consultant radiologist (Dr DC Grieve) under radiological screening following intravenous sedation using titrated doses of midazolam (2-10mg) One of three different types of stent was inserted. Streker or the more modern Ultraflex (Medi-Tech/Boston Scientific, Watertown, MA, USA) stents were deployed for proximal oesophageal strictures and tumours

requiring stenting across the G-O junction. If a fistula or perforation was suspected, a covered Wallstent (Schneider, Bulach, Switzerland) was used.

All insertions of Ultraflex/Streker stents were preceded by balloon dilation of the oesophagus using a 12mm Bluemax balloon (Medi-Tech) as recommended by the stent manufacturers. Dilatation was not considered necessary when deploying the Wallstents.

All patients undergoing a stent insertion received advice from a dietician concerning the most appropriate types of food to eat to avoid a food bolus obstruction.

Any patients with dysphagia the day following stent insertion had a contrast swallow to show an adequately stented lumen.

4.2.6 Follow-up

Following laser or intubation all patients received 40mg of omeprazole daily. Dysphagia scores and quality of life questionnaires were serially assessed at monthly intervals until death.

4.2.7 Costs

The cost of in-patient stay and treatment was based on that charged by the Western General Hospitals Trust to Fund Holding GP's. Where specific charges did not exist, the cost of the additional raw materials was added to a more basic cost code to give an overall charge. For the laser therapy, the cost of the laser fibres was added to the basic cost of an Upper GI Endoscopy. Similarly, for stenting the cost of the stent was added to the basic cost of an x-ray Session.

4.3 Ethics

Ethical approval for the study was obtained from the Lothian Research Ethics Committee. All patients gave written consent before being randomised into the trial.

4.4 Statistical analysis

It was estimated that at least thirty-six patients should be studied to define a mean difference of one point dysphagia score between the two groups at $p<0.05$ with 80% power. Analysis was undertaken on the basis of intention to treat.

Mann Whitney tests were used as appropriate.

4.5 Results

4.5.1 Patient details

The median age of the two groups, the median dysphagia score and tumour characteristics of the two groups were similar at the time of initial therapy (Table 4.1).

Table 4.1 Characteristics of patients undergoing stent or laser therapy

Characteristics	Laser(n=25)	Stent(n=27)
Male	13	13
Median age,(range)years	77 (49-90)	77 (54-90)
Median pre-treatment dysphagia score (range)	2(1-3)	2(1-4)
Site of stricture Distal Mid Proximal	 17 8	 19 7 1
Histology Squamous cell carcinoma Adenocarcinoma Anaplastic Small cell carcinoma	 9 15 1 0	 7 10 0 1

As six patients are still alive at the time of analysis they have been excluded from some of the analyses below as stated in each section.

4.5.2 Intervention

STENT INSERTION (n=27)

All stent insertions were successful. A further 4 Ultraflex stents and 4 Wallstents were placed in the laser treated patients (Table 4.2).

Table 4.2 Type of stent inserted

Type of stent	Number Inserted	Length of Stent(cm)	Diameter of stent(mm)	Number Covered
Streker/Ultraflex	4/7+4	10-15	18	
Wallstent	16+4	10.5-11	20-22	6+4

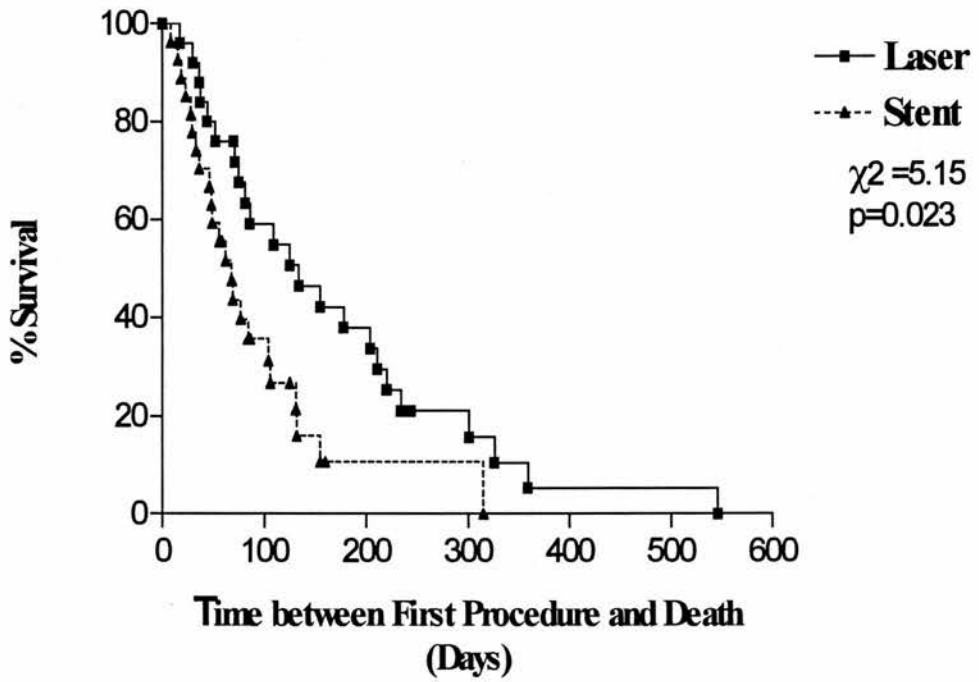
LASER TREATMENT (n=23)

For those patients now deceased, a total of 95 laser sessions were undertaken (Nd: YAG 66 sessions, Argon Diode Laser 26 sessions, Argon Plasma Coagulation three sessions). At each session the median number of Joules applied was 3221(801-8881) Joules. A total of 38 dilatations were carried out on these 23 patients giving a median of one (0-14) dilatation per patient.

4.5.3 Survival

At the time of analysis two patients in the laser treated group were still alive at 70 and 244 days and four of the stented patients at 70,86,125, and 160 days. For the remainder of patients median survival of laser patients was 125(17-546) days. This was significantly longer than that of the stented patients, 56(8-315) days, χ^2=6.8,p=0.023. (Figure 4.1). The survival advantage of the laser patients over the stented patients appears to be real and is not negated by the four stented patients who were alive at the time of analysis.

Figure 4.1 Kaplan-Meier survival curve of stent and laser treatment



4.5.4 Additional therapy (Laser=23, Stent=23)

Six patients in the laser group and eight in the stented group also received additional therapy. Four stented patients received radiotherapy, one for a metastatic spinal cord compression and two for stridor. Two patients from each group had chemotherapy with FAM. One patient in the stented group had previously had an oesophago-gastrectomy and one had previously had an Atkinson tube, which was removed due to migration. One of the laser patients had a gastrostomy tube inserted to improve nutrition.

4.5.5 Complications and recurrent dysphagia (Laser=23,Stent=23)

Five laser treated patients developed significant complications. Oesophageal perforation occurred during dilatation in one; three others developed tracheo-

oesophageal fistulae. All four patients were successfully palliated by use of covered metallic stents. One patient receiving additional chemotherapy developed neutropenia and died from pneumonia.

Four further patients randomised to laser therapy required stent insertion for recurrent dysphagia.

One patient randomised to intubation suffered a fatal stroke 24 hours after stent insertion. A further patient required injection with 1:100,000 Adrenaline into the tumour following haemorrhage. Three patients presented with a food bolus obstruction requiring disimpaction, two of whom developed aspiration pneumonia from which they did not recover. Two further patients presented with late dysphagia requiring dilatation alone (one), and laser therapy for tumour overgrowth (one).

4.5.6 Follow-up

All patients were followed up until death. This involved completion of dysphagia scores at monthly intervals. Two patients in the laser treated group and two in the stented group who were still alive at two months failed to complete the quality of life questionnaires or dysphagia scores because they were too frail or declined to. In all other patients quality of life questionnaires and dysphagia scores were assiduously completed until death.

4.5.7 Dysphagia scores

All but one laser session and all stent placements were successful. However, functional palliation of dysphagia was disappointing (Table 4.3 & 4.4). The median change in dysphagia score at one month post treatment in both groups was nought.

The figures remained similar at two and three months post-treatment, but small numbers precludes further analysis. Three patients in the laser group and one in the stented group reported an initial deterioration of swallowing at one month, which subsequently improved, and this improvement was sustained.

Table 4.3 Actual dysphagia scores at baseline and one month

Dysphagia score	Laser at Baseline	Stent at Baseline	Laser at 1/12	Stent at 1/12
0	0	0	5	0
1	5	2	4	2
2	15	18	6	10
3	5	6	4	2
4	0	1	0	0

Table 4.4 Change in dysphagia scores at one month compared to baseline

Change in Dysphagia score	Laser	Stent
-1	3	1
0	7	9
1	4	4
2	5	0

4.5.8 Hospital stay and cost

The total median number of admissions and hospital stay for the laser group were significantly longer than in the stented group (Table 4.5). This was due to the need for repeated overnight inpatient stay for those patients undergoing laser therapy.

The total mean cost of therapy in the laser group was almost double that of the stented group, again because of longer total hospital admission in the laser group.

Table 4.5 Hospital Stay and Cost Per Patient

	Laser	Stent
Median Hospital Stay(range) days	24 (5-117)	10 (2-36)
Median No. of Admissions(range)	4 (1-15)	1 (1-4)
Mean Cost of Hospital Stay(£)	4204	2278
Mean Cost of Therapy(£)	2031	1100
Total Mean Cost(£)	6235	3378

4.5.9 Quality of life

HAD

In the laser treated group 24% of patients were anxious at baseline which did not change on follow-up. Twenty-four % of lasered patients were depressed at baseline rising to 42% at one month. For the stented group, 22% of patients were anxious at baseline, which rose to 38% at one month. Forty-one % of stented patients were depressed at baseline rising to 61% at one month. (Table 4.6).

Table 4.6 Hospital Anxiety and Depression Index. Number of patients in each category according to subscale scores

Scale scores	Baseline Laser n=25	Baseline Stent n=27	One month Laser n=19	One month Stent n=13
Anxiety				
0-7	19	21	14	8
8-10	5	2	4	2
11-21	1	4	1	3
Depression				
0-7	19	16	11	5
8-10	5	3	5	4
11-21	1	8	3	4

SF36

At baseline, quality of life was globally impaired in both groups as compared to the standard general population in all domains except emotional role function and pain (Table 4.7). There was no difference between the two groups in any domain at baseline. At one month follow- up, the stented patients experienced significantly more pain and had a significantly poorer emotional role function than the laser group ($p<0.05$)

Table 4.7(1) Mean (SD) scores, Median (range) and Mann Whitney Tests for SF36 questionnaire

	Baseline Mean (SD) n=25 Laser, n=27Stent	Baseline Median(Range)	P Value(Mann-Whitney)	One month Mean (SD) n=19 Laser, n=13 Stent	One month Median(Range)	p Value(Mann-Whitney)
I Functional Status						
(a) Physical Function						
General population	79.2					
Laser	55.8(27.9)	55.0(0-100)	0.220	43.2(27.7)	45(10-90)	0.123
Stent	45.4(31.7)	40.0(0-100)		28.2(30)	20(10-90)	
(b)Social Function						
General population	78.6					
Laser	49.8(17.6)	44.4(11-89)	0.203	52.8(13.9)	55.6(22-89)	0.75
Stent	56.4(19.0)	55.6(22-100)		50(11.3)	55.6(22-67)	
(c) Role Function Physical						
General population	76.5					
Laser	25.0(27.0)	25.0(0-100)	0.634	27.5(40.5)	0(0-100)	0.15
Stent	35.2(40.0)	25.0(0-100)		3.57(9.1)	0(0-25)	
(d)Role Function Emotional						
General Population	75.0					
Laser	73.3(39.7)	100(0-100)	0.498	**65(49)**	**100(0-100)**	**0.02**
Stent	63.0(43.7)	100(0-100)		**23.8(35.6)**	**0(0-100)**	

Table 4.7(2) Mean (SD) scores, Median (range) and Mann Whitney Tests for SF36 questionnaire

	Baseline Mean (SD) n=25 Laser, n=27Stent	Baseline Median(Range)	P Value (Mann-Whitney)	One month Mean (SD) n=19 Laser, n=13 Stent	One month Median(Range)	p Value (Mann-Whitney)
II Well-being						
(a)Mental Health						
General Population	73.7					
Laser	40.0(10.3)	40(12-56)	0.714	38.8(8.8)	38(24-60)	0.42
Stent	40.3(7.2)	40(28-60)		34.6(10.6)	34(4-48)	
(b)Energy/Fatigue						
General Population	61.2					
Laser	40(16.4)	39.4(10-85)	0.884	38.7(12.4)	40(15-60)	0.93
Stent	37.4(12.9)	40(0-60)		37.1(12)	40(10-50)	
(c)Pain						
General Population	76.9					
Laser	71.1(29.2)	77.8(0-100)	0.660	**72.3(27.1)**	**78(11-100)**	**0.002**
Stent	74.9(28)	77.8(0-100)		**39(28.8)**	**33(25-85)**	
III Overall health evaluation						
General Health Perception						
General Population	68.7					
Laser	40.6(13.9)	40(8-68)	0.131	60(15.6)	62.5(50-90)	0.81
Stent	47.7(14.2)	48(24-76)		87.6(21.4)	100(25-100)	

EORTC-QLQ-C30

There was no significant difference between the two groups in any category at the baseline assessment (Table 4.8 & 4.9). At one month the stented group experienced significantly more loss of appetite than the laser group.

Table 4.8 Median scores and interquartile ranges of functional and global health scales (EORTC- QLQC30)

	Baseline			**One Month**		
	Laser n=25	Stent n=27	p Value (Mann-Whitney)	Laser n=19	Stent n=13	p Value (Mann-Whitney)
Functional Scales						
Physical Functioning	40 (20-80)	60 (20-80)	0.833	40 (20-80)	20 (0-60)	0.447
Role Functioning	66.7 (33-92)	50 (17-83)	0.415	50 (17-88)	17 (0-83)	0.149
Emotional Functioning	83 (67-100)	83 (58-100)	0.469	83 (75-100)	62 (44-87)	0.083
Cognitive Functioning	83 (50-100)	83 (67-100)	0.687	83 (62-100)	67 (50-92)	0.262
Social Functioning	67 (33-92)	67 (50-100)	0.993	67 (33-100)	33 (17-67)	0.06
Global Health Status/QOL						
Global Health Status	50 (21-62)	42 (17-50)	0.486	46 (17-67)	33 (17-58)	0.841

Table 4.9 Median scores and interquartile ranges of symptom scales, symptom items (EORTC-QLQC30)

	Baseline			**One Month**		
Symptom Scales	Laser	Stent	P value (Mann Whitney)	Laser	Stent	p Value (Mann Whitney)
Fatigue	44 (17-67)	44 (11-67)	0.964	44 (30-67)	78 (39-94)	0.075
Nausea and Vomiting	33 (0-50)	33 (17-33)	0.763	33 (0-37)	33 (12-71)	0.239
Pain	17 (0-42)	17 (0-50)	0.647	25 (0-50)	50 (17-75)	0.114
Single Items						
Dyspnoea	0 (0-33)	0 (0-33)	1.00	17 (0-67)	33 (0-75)	0.314
Insomnia	0 (0-67)	33 (0-67)	0.292	0 (0-33)	33 (0-67)	0.102
Appetite loss	67 (17-100)	67 (0-100)	0.805	**50 (33-75)**	**100 (67-100)**	**0.024**
Constipation	0 (0-33)	33 (0-67)	0.369	33 (0-42)	33 (33-67)	0.149
Diarrhoea	0 (0-0)	0 (0-0)	0.667	0 (0-8)	0 (0-0)	0.734
Financial Difficulties	0 (0-0)	0 (0-0)	0.487	0 (0-0)	0 (0-33)	0.055

EORTC-QLQ-OES24

At baseline there were no significant differences between the two groups in any of the domains (Table 4.10). At one month follow-up, there were significant differences between the stented and laser groups in four categories. Stented patients experienced significantly more pain, indigestion and a bad taste in the mouth than the laser treated patients. Laser treated patients again reported a significantly better emotional function.

There was no significant change in the dysphagia, deglutination or eating scores for each group from baseline.

Table 4.10 Median scores and interquartile ranges of symptom scales and single items (EORTC-OES24)

	Baseline			**One Month**		
Symptom Scales	Laser n=15	Stent n=16	P value (Mann Whitney)	Laser	Stent	p Value (Mann Whitney)
Dysphagia	44 (33-56)	56 (44-67)	0.144	33 (17-67)	56 (39-72)	0.24
Deglutition	0 (0-17)	17 (0-29)	0.452	8 (0-17)	0 (0-42)	1.00
Eating	17 (8-67)	38 (25-65)	0.055	25 (0-50)	50 (25-96)	0.07
Indigestion	0 (0-22)	11 (0-22)	0.502	**0 (0-11)**	**33 (0-78)**	**0.05**
Pain	22 (0-22)	11 (0-33)	0.984	**11 (0-22)**	**33 (11-72)**	**0.04**
Emotional	83 (67-92)	67 (44-81)	0.220	**83 (65-94)**	**25 (4-54)**	**0.004**
Single items						
Dry mouth	33 (0-33)	33 (8-68)	0.167	33 (0-67)	67 (0-100)	0.49
Troublesome taste	0 (0-33)	17 (0-67)	0.236	**0 (0-25)**	**67 (33-83)**	**0.02**
Troublesome coughing	0 (0-0)	0 (0-58)	0.167	0 (0-33)	33 (0-50)	0.12
Troublesome talking	0 (0-0)	0 (0-25)	0.179	0 (0-33)	0 (0-50)	0.54

4.6 Discussion

The aim of palliation in advanced oesophageal cancer is to overcome dysphagia and optimise quality of life using interventions that have minimal complications. Our series, like all others, has demonstrated how difficult this is to achieve.

The relief of dysphagia was disappointing and similar in patients treated by laser therapy or intubation. Most patients reported no change in their overall quality of swallowing one month after intervention and those who survived for several months also stated that dysphagia persisted. This contrasts to the study reported by Adam et

al [269] who reported a median of two-point improvement in dysphagia score in patients intubated with expandable stents, compared to a median improvement of one point in laser patients.

The disappointing results may be due to inclusion of an older, frailer group of patients with more advanced disease and this is supported by the very poor survival of both patient groups. It may also be due to the method of assessment which was by independent patient completed questionnaire, as compared to physician assessment. Blazeby et al have shown that there is poor correlation between doctors and patients assessment of dysphagia [281]. Unlike other series, the "best dysphagia score" was not recorded. This can be extremely short-lived and in our view is probably not a good measure of significant benefit. Nevertheless, dysphagia did not generally progress in either group and no patient died with absolute dysphagia.

Significant complications occurred after laser and intubation. It is likely that prior radiotherapy contributed to the single oesophageal perforation that occurred in this trial; endoscopists should be wary of dilatation following radiotherapy. It is possible that oesophago-bronchial fistulae, observed in three patients, were a consequence of repeated laser therapy. All of these occurred after multiple treatment sessions. Stent migration, which has been a relatively commonly reported event following insertion of stents across the gastro-oesophageal junction [253;321], did not occur in this series, possibly because Wallstents were not deployed at this site.

Late complications included recurrent dysphagia and some patients were crossed-over to the alternative treatment option resulting in alleviation of dysphagia. It is important that both stenting and ablative therapy are available when dealing with advanced oesophageal cancer. Tumour in- or over-growth following stenting is

probably best treated by laser, whilst fistulating and extensive circatrising tumours are best managed by intubation.

In the trial the median survival of laser treated patients was significantly longer than that of intubated patients. This has also been reported in another small study [271]. This observation may be an anomaly related to small sample size. It could alternatively be due to tumour debulking or to a biological response following laser induced tissue damage. A larger study is needed to confirm or refute the survival benefit of laser palliation.

The major purpose of the interventions examined in this trial was to improve quality of life rather than to prolong survival. Quality of life in advanced oesophageal cancer is the product of several inter-relating factors including the degree of dysphagia, pain and other physical symptoms and the psychological response to the disease. Other studies have demonstrated that relief of dysphagia and improved well being are poorly correlated [294;296;322] and this was confirmed in our trial.

Collecting complete and accurate QOL data is not easy and several practical difficulties arise particularly in an elderly and frail population. Other studies measuring QOL in patients with oesophageal cancer have reported compliance rates of 30-92%[270;294;295;322]. In this study, the combination of all of the questionnaires was relatively long (106 questions). The compliance rate was 92%, two patients from each group failing to complete the questionnaires at one month; all other patients completed the questionnaires assiduously until just before death. This compliance rate may have introduced biases into the quality of life data.

The generic questionnaires used in this study did, as expected, reveal significant abnormalities in most patients. The findings of the SF36 and the EORTC-QLQC30

were very similar, with global reductions in most aspects with particularly severe reduction in mental health, lethargy and physical role function. Because survival was so poor, the follow-up data were only meaningful for the first month after intervention and it is noteworthy that at this time pain was more prominent in the stented patients compared to the laser treated group. This may be related to pressure effects exerted by the expanding stent upon mediastinal structures and was a surprising but consistent finding. Pain following stent insertion tended to ease in the few long term survivors after the first month.

The EORTC oesophageal module (OES24) revealed stented patients had more pain, indigestion and troublesome taste at one month than the laser patients. The OES24 has been designed to increase the sensitivity and specificity of the EORTC QLQ C-30 for patients with oesophageal cancer. It was able to reveal changes in Quality of Life that other more crude measures failed to detect. As it has been recently developed there is no literature on its use in clinical trials. However, it may prove to be a useful tool to measure of quality of life in patients with oesophageal cancer in future trials.

The information that the QOL questionnaires provided was clearly limited by poor survival in this study, but these tools are user-friendly and provide useful information concerning over-all well being. The degree of anxiety, measured by the HAD questionnaire, varied widely but about a quarter of patients in both groups had case-level anxiety at the time of randomisation. This level had increased in the stented group at one month. A proportion of patients in each group were also depressed, and this had increased in both stented and laser treated patients at one

month. It may in future be useful to identify those patients who score highly for anxiety or depression and offer specific intervention at any early stage.

This study has emphasised the difficulties encountered in palliation of advanced oesophageal cancer. Future studies should measure quality of life issues, in addition to the assessment of dysphagia.

CHAPTER 5- Radical radiotherapy for oesophageal cancer

5.1 Introduction

Radiotherapy has several potential roles in the treatment of oesophageal cancer. These include high dose, radical radiotherapy which attempts cure, adjuvant peri-operative radiotherapy to 'down-stage' tumours and improve the chance of cure by surgical resection, and lower dose palliative radiotherapy which may relieve dysphagia with minimal side effects but little effect upon survival.

In this chapter the efficacy of radical radiotherapy is addressed. The trial reported by Pearson et al from the Western General Hospital influenced clinical practice for two decades [323]. This large retrospective analysis reported a one year survival rate of 44% and a 5 year survival rate of 22% for patients treated by radical radiotherapy alone for oesophageal cancer. Twenty-five years later it was felt appropriate to review this approach using a subsequent cohort, treated in the same institute.

Unfortunately, the early encouraging results of radical radiotherapy for oesophageal cancer have never been reproduced. Earlam and Cunha-Melo reviewed more than 8000 patients treated by radiotherapy alone (some palliative) reported in 49 articles in the period between 1954 and 1979. This was not a meta-analysis and they calculated the mean 5-year survival of all these studies as 6%[324]. Palliation of dysphagia was achieved in the majority of patients, but may take several weeks, and up to 40% of patients developed a recurrent malignant stricture. In general, patients selected for radiotherapy have a poor prognosis, either due to co-morbid disease, locally advanced or metastatic disease.

Adenocarcinoma of the oesophagus has often been considered to be radioresistant, but there are data showing little difference in survival rates between patients with adenocarcinoma and those with squamous carcinoma affecting the cardia treated with radiotherapy [204]. This is particularly relevant because adenocarcinoma of the oesophagus and cardia are increasing in incidence. The use of radiotherapy in the potentially curative setting requires doses of at least 5000cGy at 180-200cGy/fraction.

Many more recent series have reported results of external beam radiation therapy alone for oesophageal carcinoma. The majority of these series include patients with unfavourable features such as lymph node involvement or locally advanced disease. For example, in the study by De-Ren 184 of the 678 patients had stage-IV disease [325]. Overall, the 5 year survival for patients with carcinoma of the oesophagus treated with radiation therapy alone was approximately 10% (Table 5.1).

Table 5.1 Comparison of studies of radiation therapy alone for oesophageal cancer

Reference	Histology	Stage	No. of patients	5-year survival (%)
Newaishy 1982 [326]	Squamous	Inoperable	444	9
Okawa 1989 [327]	Squamous	I II III IV	43 130 92 23	20 10 3 0
De-Ren 1989 [325]	Various	II III	177 501	22 28

Okawa et al have suggested that therapeutic results with radiation alone may only equal those of surgery for T1 tumours [328]. They treated 21 patients with T1-N0-M0 squamous cell carcinoma who refused surgery, or had significant co-morbidity with a median total dose of 70Gy (range 50-76Gy). The five-year cause specific survival

was 61.7%. Five patients had in-field local lymph node recurrence and another three had lymph node recurrence outside the treatment field. The treatment was well tolerated. Fourteen patients developed mild and two moderate oesophagitis.

The morbidity of radiotherapy depends on the dose, the technique, and whether the patient received chemotherapy or underwent surgery. There are very limited toxicity data presented in most series. An exception is the control arm of the RTOG 85-01 study in which acute-radiation-related morbidity is well documented [206;329]. In this study, 60 patients received radiation therapy alone to a dose of 6400cGy. Acute grade-III toxicity was 25%, and grade-IV toxicity was 3%. There were no treatment-related deaths. Similarly, there are few reports of long-term radiation morbidity. In general patients who receive radiation therapy alone have a 30-60% incidence of oesophageal stricture, and almost half of these are associated with local recurrence [330].

Locoregional failure remains one of the major problems for patients with oesophageal cancer even after curative radiotherapy. In an analysis of six studies, persistent or recurrent tumours were found in 56-85% of cases [331]. Neck and mediastinal relapses occurred in 10-43% of cases and distant metastasis was documented in 36-50% of cases. It has been surmised that one of the reasons for this high relapse rate is that oesophageal cancers have a short potential doubling time allowing repopulation of tumour cells during fractionation. Nishimura et al have demonstrated a benefit of decreasing the treatment period with respect to local tumour control [332]. In this twice- daily treatment regime, 64 to 68Gy was given in 4 weeks instead of the conventional 6 weeks, resulting in local control rates at 1 year of 47% versus 22%. Ten out of the 36 patients in the accelerated group developed

benign stenosis. The authors conclude that total treatment time might have a significant impact on local cure.

In order to shorten overall treatment time without causing acute toxicity, accelerated radiotherapy has been given using a concomitant boost technique. In one study, 88 patients with oesophageal cancer, ineligible for surgery were given accelerated fraction radiotherapy [333]. In addition 64% of patients had neoadjuvant chemotherapy. Sixteen percent of patients experienced grade 3 oesophagitis, and oesophageal stenosis occurred in 8% of patients. Multivariate analysis demonstrated that T stage and overall treatment time were prognostic factors for cause-specific survival. T stage and neoadjuvant chemotherapy were independent adverse prognostic factors for locoregional control.

The combination of chemotherapy and radiotherapy is based on the ideas of enhanced antitumour activity and independent toxicity.

There are a number of single-armed trials of combined modality therapy alone for oesophageal cancer [208,334-337]. In the trial reported by Coia, patients with stage I and II disease were treated and analysed separately. Patients received 5-FU and mitomycin C concurrently with 6000cGy. Combining stages I and II, the local failure rate was 25% and the 5-year survival rate was 30%.

Four randomised trials have compared radiation therapy alone with combined modality therapy [206,338-340]. Unfortunately in three of the four trials inadequate doses of systemic chemotherapy were delivered. The trial of the Radiation Therapy Oncology Group [206] was the only one designed to deliver adequate doses of systemic chemotherapy with concurrent radiation therapy. Patients had squamous cell carcinoma and received four cycles of 5-FU and cisplatin. Radiation therapy

(5000cGy) was given concurrently with chemotherapy, beginning on day 1. Only about half the patients completed the four cycles of chemotherapy. The control group received 6400 cGy of radiation therapy alone. At two years, patients who received combined-modality therapy showed a significant improvement in survival (38% Vs 10%) as well as significant decreases in local failure (44% Vs 65%) and distant failure (12% Vs 26%). With longer follow-up the 3-year survival in the combined modality group was 31%. There were no three-year survivors in the radiation therapy control arm [329]. Following this Poplin et al have reported the results of intensive treatment consisting of high-dose radiotherapy (40 to50Gy) and four courses of concurrent continuous infusion of 5-FU and cisplatin in 26 patients with oesophageal cancer [341]. Survival at 1 and 2 years was 65% and 50% respectively, and the median survival of the patients with a complete response was over 37 months. Only 12 patients received the prescribed dose of chemotherapy owing to treatment toxicity. The authors concluded that a high frequency of local tumour resolution was achieved at the cost of significant toxicity.

The Eastern Co-operative Oncology Group performed a similar randomised trial of radiation therapy alone versus combined modality therapy [342]. Patients had the option of surgery after receiving 4000cGy, making the results more difficult to interpret. An interim analysis revealed a significant improvement in median survival (14.9 months versus 9 months) for patients who received combined-modality therapy.

5.2 Methods

Patients given a complete course of curative external beam radiotherapy (EBRT) (20 fractions to a total minimum dose of 4500cGy) for oesophageal cancer between 1989 and 1996 were identified from the database in the department of oncology, and their records were reviewed. Details available directly from the database were age, histology, site, date of the start of treatment, dose and number of fractions of EBRT and the date of death. Examination of the notes enabled further information to be obtained including complications of treatment, concomitant therapies and cause of death. Descriptions of swallowing, as assessed by a physician, both before and after treatment were taken from the notes. These were converted a four-point scale comprising normal swallowing, difficulty with some solids, soft diet, liquid diet and complete dysphagia.

5.3 Results

5.3.1 Patient Details

A total of 60 patients having radiotherapy with curative intent were identified. Seventeen failed to complete the complete course of 20 fractions. Of the remaining 43 patients treated within this period, it was possible to obtain the hospital records of 41. Twenty -two of the patients were male, with a median age of 71 (range 53-85) years. Histology in the majority of patients showed squamous cell carcinoma and the site of the tumour was most commonly proximal (Table 5.2). The median length of the tumour recorded in 33 patients was 5 (range 1-10) cms. Pre-treatment assessment with either ultrasound scan or CT scan revealed 4 patients with local

tumour invasion, 6 with lymph node involvement and 1 with a metastasis. The median dose of EBRT was 5200 (range 4500-5488) cGy given in 20 fractions over 30 days.

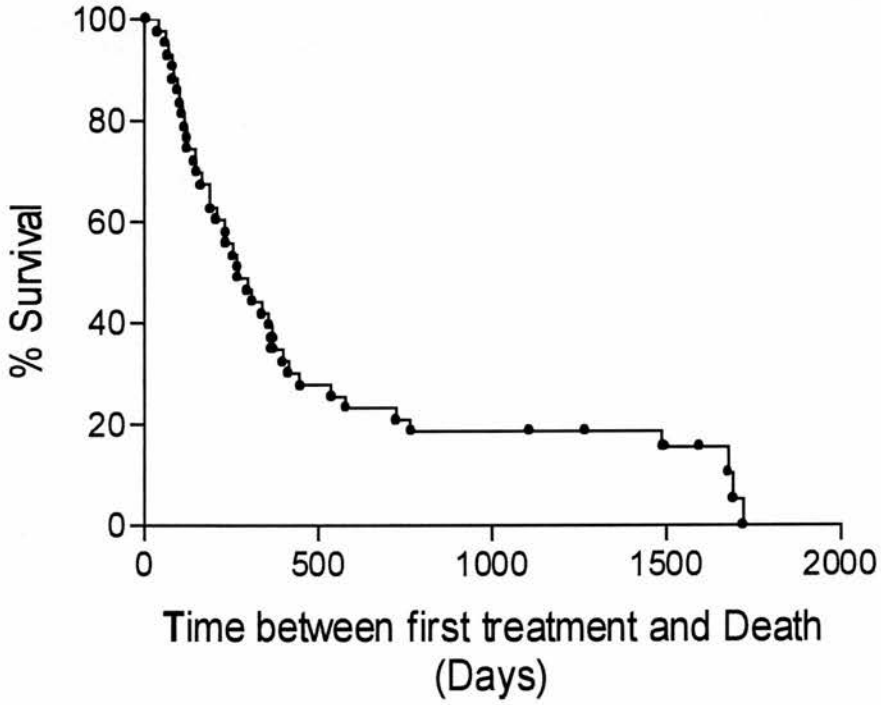
Table 5.2 Patient Details

Male	22
Median age,(range)years	71(53-85)
Median pre-treatment dysphagia score (range)	2(0-4)
Site of stricture	
Distal	8
Mid	13
Proximal	22
Histology	
Squamous cell carcinoma	34
Adenocarcinoma	5
Small cell cancer	1
Undifferentiated cancer	2
Spindle cell cancer	1

5.3.2 Survival

At the time of analysis 4 patients are still alive at 1591,1270,1494 and 1107 days. For the remaining patients median survival was 255(range 42-1722) days (Figure). Thirty-two patients died from carcinomatosis, five from other causes and two from unknown causes. This gives a one-year survival of 40%, a two-year survival of 21% and a five-year survival of 0%.

Figure 5.1 Kaplan-Meier survival curve of curative radiotherapy for oesophageal cancer



5.3.3 Tumour Recurrence and Complications

Eighteen (44%) patients had either a local or metastatic recurrence of disease at a median of 195.5 (range 63-1207) days. During therapy, 10 (24%) patients suffered from either oesophagitis or retrosternal chest pain and a further 11(27%) patients reported a marked deterioration in their swallowing. Other complications of therapy included 6(15%) patients with post-radiation strictures and 4(10%) with either tracheo-oesophageal fistula or oesophageal perforation.

5.3.4 Additional Therapy

Two patients had concomitant chemotherapy one with 5FU and the other with MCVP 16. A further eighteen patients received a total of 23 additional therapies (Table 5.3)

Table 5.3 Additional therapies

Type of Therapy	No. of Patients	Comments
Oesophageal Dilatation	10	
Gastrostomy Feeding Tube	2	
Oesophageal Intubation *Expandable metallic stent* *Plastic tube*	 3 5	
Radiotherapy	3	2 for lymph node involvement 1 for intratracheal tumour

5.3.5 Dysphagia

Assessment of dysphagia score was possible in 39 (91%) patients, prior to and one month following treatment (Table 5.4). Twelve patients showed an improvement in their dysphagia score by at least one point, 17 reported no change in swallowing and 10 patients reported deterioration in swallowing by at least one point.

Table 5.4 Dysphagia Scores

Dysphagia score	Baseline	One Month
0	6	11
1	10	3
2	12	17
3	10	7
4	1	1

5.4 Discussion

EBRT provides the possibility of cure for those patients presenting with oesophageal cancer who are unsuitable for radical surgery either because of comorbidity or locally advanced disease.

This study examining the use of curative EBRT alone in 43 patients with oesophageal cancer is limited by its retrospective nature. It reveals a five-year survival of 0%, which is much poorer than other studies that have been reported in the literature. Based on staging by ultrasound or CT scan these patients appeared to be in a good prognostic group. However, staging based purely on these modalities is crude compared with more sensitive investigations such as endoscopic and laparascopic ultrasound. It is likely that a number of patients in this study were understaged at initial presentation contributing to the poor survival. In the future it may be possible to use other techniques to identify patients with oesophageal cancer who will do well after radiotherapy. For example, Pomp et al have measured p53 using immunohistochemistry in patients with oesophageal cancer treated with radiotherapy alone and showed that p53 overexpression was an independent prognostic factor [343].

The technique of EBRT involving administration of 5000Gy over 30 days is a fairly standard technique. Survival can be enhanced if adjuvant chemo- and brachy-therapy are used. It may no longer be appropriate to give EBRT alone to patients with potentially curable oesophageal cancer.

Survival has traditionally been the main outcome measure for the assessment of potentially curative treatments. In the case of oesophageal cancer, where even

curative modalities result in a poor 5-year survival, other measures such as quality of life and dysphagia should be more rigorously assessed and considered.

The high rate of tumour recurrence, either local or metastatic, of 44% is similar to that reported in the literature [331]. It may reflect initial failure to select patients in whom there was really a possibility of cure or alternatively it may indicate limitations of the treatment. As discussed previously, the rapid tumour doubling time may allow repopulation of cells between radiotherapy fractions.

A high dose of EBRT results in a high complication rate. Acute complications of oesophagitis or worsening dysphagia occurred during treatment in half of the patients. A further 25% required additional therapies to overcome the later complications of post radiation stricture and tracheo-oesophageal fistula. Again, these complication rates are similar to those reported elsewhere [330].

Assessment of dysphagia was made purely from comments in the medical records and translated onto the four-point dysphagia scale. Obviously this is a crude analysis and also reflects the bias of a physician based rather than patient based assessment. It has previously been shown that there is very poor correlation between doctors and patients ratings of dysphagia [281]. Reported improvement in swallowing at one month was disappointing and may reflect the high incidence of oesophagitis that was reported. Longer term swallowing was more difficult to assess as it was recorded erratically in the notes, but would have been affected by both the occurrences of post radiation strictures and local recurrence.

As several studies have shown improved survival rates without greater toxicity using combination EBRT with either chemotherapy or brachytherapy for patients with

potentially curable oesophageal cancer unsuitable for surgery, future research should be directed towards refining these techniques. Other aspects of the disease should also be considered and care of patients should also involve dieticians and palliative care specialists. In a disease where currently survival with any treatment is poor, further studies need to include outcome measures such as quality of life and dysphagia scores.

CHAPTER SIX- Summary and Conclusions

This thesis examines aspects of the treatment and prevention of oesophageal cancer. Currently oesophageal cancer is becoming an increasing clinical problem due to its rapidly rising incidence. If current rates of increase continue, this disease will require more and more resources and expertise.

Barrett's oesophagus provides a model of cancer progression in a site, which allows comparatively easy access to tissue specimens. Research into Barrett's oesophagus is therefore relevant to our broader understanding of carcinogenesis and is obviously relevant to oesophageal cancer particularly in the face of its rapidly increasing incidence. The idea of reducing the incidence of oesophageal adenocarcinoma by eradication of Barrett's oesophagus is an attractive one. The ideal treatment is one, which is easily administered, easily tolerated, with little morbidity, reliably ablates all Barrett's mucosa and is shown to reduce the cancer risk. Currently endoscopic therapies are a long way from this ideal, but in the face of a fatal disease, which has a potentially curable precursor strenuous efforts need to be made to refine these techniques. So far different techniques have either shown incomplete ablation of the Barrett's mucosa, for example APC, [319] or been associated with a high oesophageal stricture rate due to underlying muscle damage, for example PDT [153]. Bown suggests in a recent editorial that further improvement in results with APC is unlikely due to the difficulty of applying it consistently to the whole of the mucosa surface [344]. He suggests that PDT, although requiring more research to develop a photosensitising agent causing the optimum depth of mucosa necrosis without causing muscle damage, has the better potential for treating the mucosa uniformly.

The effect on cancer risk for such endoscopically treated patients, even in the presence of a few remaining glands is unknown. The answer to this question can only be obtained through follow-up of a large number of treated patients over many years. Meanwhile, we are left with the option of screening patients with Barrett's oesophagus with the hope of picking up early tumours at a curable stage. As this represents a considerable practical undertaking it would be sensible to limit screening to patients with Barrett's oesophagus identified as being at particularly high risk for the development of a carcinoma. p53 staining and flow cytometry can give an indication towards increased cancer risk, but are unable to reliably predict individuals with Barrett's oesophagus who will develop an oesophageal cancer. Certainly this should be a continuing area for research. As more endoscopic therapies are developed, p53 staining and flow cytometry may provide more information on the efficacy of such treatments before reduction in cancer risk can be assessed.

Despite several theories, the aetiology of the rise in incidence of oesophageal cancer needs to be explored further. More research needs to be undertaken into the impact of proton pump inhibitors and Helicobacter Pylori infection on the development of Barrett's oesophagus and oesophageal adenocarcinoma.

Oesophageal cancer is a cause of considerable morbidity and mortality. Initial assessment should involve new and rigorous methods of disease staging such as endoscopic and laparoscopic ultrasound. These techniques enable accurate staging of disease and permit tailoring of treatment, whether curative or palliative to the individual patient. Unfortunately, patients tend to present with advanced disease and only a third of patients are potentially curable at this time. Education of the general

public, and general practitioners about the symptoms of oesophageal cancer has been a neglected area. As it increases in incidence, such information may encourage patients to present early with symptoms of dysphagia and enable more patients to present with potentially curable disease.

Most treatment studies have focussed on curative treatments for oesophageal cancer, but such studies are relevant to only one third of patients with this disease. More emphasis and research needs to be placed on methods of palliation. Palliative therapy involves a multi-disciplinary approach involving, physicians, surgeons, radiologists, oncologists and nutritionists. Standard routes of referral and treatment for such patients need to be more clearly established than at present. Further good randomised studies comparing different forms of palliation need to be performed so that the optimum treatment can be offered to all individuals. Collaboration between different specialities will enable combination therapies, such as radiotherapy and stenting to be assessed. Treatment should not purely focus on the relief of dysphagia but should also aim to optimise other aspects of health related quality of life.

For a disease with poor survival it is not good enough to look only at survival as an endpoint for studies examining different therapies. The quality of life achieved by such treatments also needs to evaluated. Measuring quality of life has many inherent problems. It is generally very time consuming and requires considerable patience on the part of both the interviewer and patient. Many patients with oesophageal cancer are very frail and elderly and can find such questionnaires difficult to complete. Performed serially they can give useful information for the individual patient. Performed in the context of treatment studies, they enable broader conclusions to be reached.

In order to enable comparison between studies, similar well validated questionnaires need to be used. The development of the EORTC-OES24 questionnaire goes a long way to making the measurement of quality of life relevant to the particular problems and concerns of patients with oesophageal cancer.

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APPENDICES

APPENDIX ONE

ASSESSMENT OF HOW YOU ARE FEELING

For each question please tick the answer which matches best how you feel

1) I feel tense or "wound up"
- Most of the time.....
- A lot of the time.....
- Time to time, occasionally.....
- Not at all.....

2) I still enjoy the things I used to enjoy
- Definitely as much.....
- Not quite as much.....
- Only a little.....
- Hardly at all.....

3) I get a sort of frightened feeling as if something awful is about to happen
- Very definitely and quite badly.....
- Yes, but not too badly.....
- A little, but it doesn't worry me.....
- Not at all.....

4) I can laugh and see the funny side of things
- As much as I always could.....
- Not quite so much now.....
- Definitely not so much now.....
- Not at all.....

5) Worrying things go through my mind
- A great deal of the time.....
- A lot of the time.....
- From time to time but not too often.....
- Only occasionally.....

6) I feel cheerful
- Not at all.....
- Not often.....
- Sometimes.....
- Most of the time.....

7) I can sit at ease and feel relaxed
- Definitely.....
- Usually.....
- Not often.....
- Not at all.....

8) I feel as if I am slowed down
- Nearly all the time.....
- Very often.....
- Sometimes.....
- Not at all.....

9) I get a sort of frightened feeling like butterflies in the stomach
- Not at all.....
- Occasionally.....
- Quite often.....
- Very often.....

10) I have lost interest in my appearance
- Definitely.....
- I don't take quite so much care as I should.....
- I may not take quite as much care.....
- I take just as much care as ever.....

11) I feel restless as if I have to be on the move
- Very much indeed.....
- Quite a lot.....
- Not very much.....
- Not at all.....

12) I look forward with enjoyment to things
- As much as ever I did.....
- Rather less than I used to.....
- Definitely less than I used to.....
- Hardly at all.....

13) I get sudden feelings of panic
- Very often indeed.....
- Quite often.....
- Not very often.....
- Not at all.....

14) I can enjoy a good book or radio or TV programme
- Often.....
- Sometimes.....
- Not often.....
- Very seldom.....

APPENDIX TWO

ASSESSMENT OF OVERALL HEALTH STATE
(SF36)

1) In general would you say your health is: (Tick one box)

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

2) Compared to one year ago, how would you rate your health in general now? (Tick one box)

Much better than 1 year ago	☐
Somewhat better now than 1 year ago	☐
About the same as 1 year ago	☐
Somewhat worse than 1 year ago	☐
Much worse than 1 year ago	☐

3) The following items are about activities you, might do during a typical day. Does your health limit you in these activities? If so how much? (Tick one box on each line)

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a) Vigorous activities, such as running, lifting heavy objects, particpating in strenuous sports	☐	☐	☐
b) Moderate activities, such as moving a table, pushing a vacuum cleaner, or playing golf	☐	☐	☐
c) Lifting or carrying groceries	☐	☐	☐
d) Climbing several flights of stairs	☐	☐	☐
e) Climbing one flight of stairs	☐	☐	☐
f) bending, kneeling or stooping	☐	☐	☐
g) Walking more than a mile	☐	☐	☐
h) Walking more than half a mile	☐	☐	☐
i) Walking one hundred yards	☐	☐	☐
j) Bathing or dressing yourself	☐	☐	☐

4) During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of your physical health?

	yes	no
a) Cut down the amount of time you spent on work or other activities	☐	☐
b) Accomplished less than you would like	☐	☐
c) Were limited in the kind of work or other activities	☐	☐
d) Had difficulty performing the work or other activities (for example it took extra effort)	☐	☐

5) During the past 4 weeks, have you had any of the following problems with your work or other regular activities as a result of any emotional problems (such as feeling depressed or anxious)

a) Cut down the amount of time you spent on work or other activities	☐	☐
b) Accomplished less than you would like	☐	☐
c) Didn't do work or other activities as carefully as usual	☐	☐

6) During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

7) How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

8) During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

9) How much time during the past 4 weeks.....

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
a) Did you feel full of life?	☐	☐	☐	☐	☐	☐
b) Have you been a very nervous person?	☐	☐	☐	☐	☐	☐
c) Have you been so down in the dumps that nothing could cheer you up?	☐	☐	☐	☐	☐	☐
d) Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
e) Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
f) Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐
g) Did you feel worn out?	☐	☐	☐	☐	☐	☐
h) Have you been a happy person?	☐	☐	☐	☐	☐	☐
i) Did you feel tired?	☐	☐	☐	☐	☐	☐
j) Has your health limited your social activities (like visiting with firends or close relatives)?	☐	☐	☐	☐	☐	☐

10) During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives etc)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

11) Please choose the answer that best describes how TRUE or FALSE each of of the statements is for you.

	Definitely true	Mostly true	Not sure	Mostly false	Definitely false
a) I seem to get sick a little easier than other people	☐	☐	☐	☐	☐
b) I am as healthy as anybody I know	☐	☐	☐	☐	☐
c) I expect my health to get worse	☐	☐	☐	☐	☐
d) My health is excellent	☐	☐	☐	☐	☐

APPENDIX THREE

EORTC QLQ-C30 (version 2.0.)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your inititals: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|

		No	Yes
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2.	Do you have any trouble taking a long walk?	1	2
3.	Do you have any trouble taking a short walk outside of the house?	1	2
4.	Do you have to stay in a bed or a chair for most of the day?	1	2
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - OES 24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Could you eat solid foods?	1	2	3	4
32. Could you eat liquidised or soft foods?	1	2	3	4
33. Could you drink liquids?	1	2	3	4
34. Have you had trouble swallowing your saliva?	1	2	3	4
35. Have you choked when swallowing?	1	2	3	4
36. Have you had trouble enjoying your meals?	1	2	3	4
37. Have you felt full up too quickly?	1	2	3	4
38. Have you had troublesome eating?	1	2	3	4
39. Have you had troublesome eating in front of other people?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you had problems with your sense of taste?	1	2	3	4
42 Have you had troublesome coughing?	1	2	3	4
43. Have you had troublesome talking?	1	2	3	4
44. Have you had troublesome belching?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
47. Have you had pain when you eat?	1	2	3	4
48. Have you had pain in your chest?	1	2	3	4
49. Have you had pain in your stomach?	1	2	3	4
50. Have you worried about your weight being too low?	1	2	3	4
51. How much has your treatment been a burden to you?	1	2	3	4
52. How much has your illness been a burden to you?	1	2	3	4
53. Were you worried about your health in the future?	1	2	3	4
Complete this question only if you had hair loss 54. Were you upset by the loss of your hair?	1	2	3	4